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Studies on the Synthetic Aspects of Fluoromethylmetal Reagents Derived from Tribromofluoromethane

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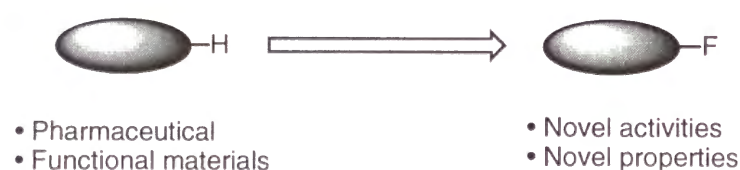
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Chapter 1

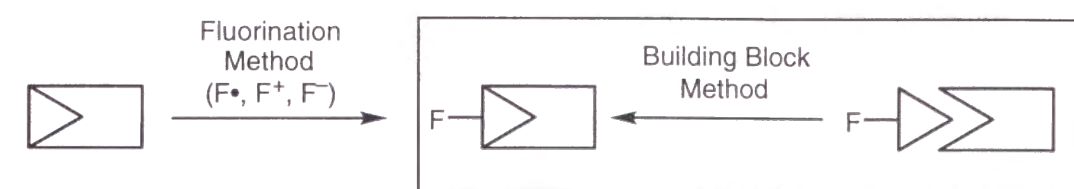
General Introduction

More than one hundred years have passed since fluorine was isolated by Moissan in 1886. The fluorine chemistry has remarkably advanced starting with hydrogen fluoride, the most basic reagent. Hydrogen fluoride is now converted into various metal fluorides, sulfur fluorides, and ammonium fluorides that are inevitable in the field of electric, construction, and automobile industries. Particularly, perfluorinated materials¹⁾ of gaseous, liquid and solid phases have assisted the improvement of the quality of life due to their unique properties. Recently, partially fluorinated compounds are shown to enhance biological activities due to increased stability and lipophilicity and also owing to mimic and block effects by fluorine.²⁾ Therefore, organofluorine compounds have recently been attracting more attention in the fields of pharmaceutical, agrochemical, and material sciences.²⁾ Since the biological activities and characteristic properties relate closely to fluorine functionality, development of effective, selective synthetic methods for organofluorine compound is a matter of urgency.



There are two methods for the synthesis of organofluorine compounds: direct fluorination and building block approach.³⁾ Direct fluorination method usually uses hydrogen fluoride or fluorine gas that is particularly effective for the synthesis of perfluorinated compounds but, in general, too reactive. In handling these reagents, special equipments should be employed with great care. To achieve the fluorination more conveniently, a variety of electrophilic reagents including a hetero atom-fluorine bond are invented.^{3,4)} On the other hand, nucleophilic fluorination is effected using fluoride reagents. Nucleophilic fluorination with a fluoride ion under electrophilic activation of substrates is a more convenient method. A typical example is oxidative desulfurization-fluorination⁵⁾ that attains selective fluorination under mild conditions.

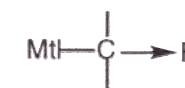
In contrast, building block approach⁶⁾ uses a variety of relatively low molecular weight halofluoro carbons that are commercially readily available. This method is particularly useful for organic chemists, because it is much easier to control the position and configuration of fluorine functionality.



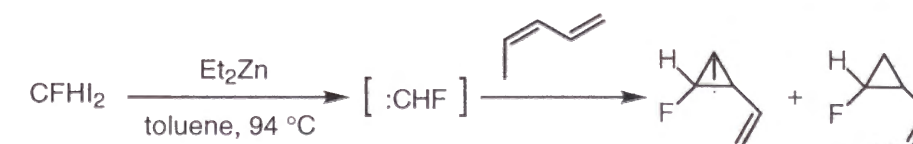
Although many methods are available for the incorporation of a fluorine building block into substrates, organometallic reagents generated from polyhalofluoromethanes are useful particularly for the synthesis of monofluoro compounds. The reagents are easily prepared by halogen-metal exchange⁷⁾ or deprotonation.⁸⁾ In addition, carbon-halogen bond(s) remaining in products can further be converted into carbon-carbon bond(s)⁹⁾ and/or various carbon-heteroatom bond(s).¹⁰⁾ Today, various kinds of polyhalofluoromethanes are commercially available.

Fluorohalomethylmetal reagents,¹¹⁾ once prepared easily, should serve as a versatile C₁ unit of organofluorine compounds. However, in general, fluorohalomethylmetal reagents are thermally labile to undergo α -elimination through intramolecular coordination to metal by a leaving halogen and generate electrophilic carbenes.¹²⁾ The instability of a fluoromethylmetal reagent is attributed to the repulsion between electrons in *p*-orbitals of fluorine and anionic carbon.^{6b,13)} This effect overrides the inductive (-I) effect of fluorine.

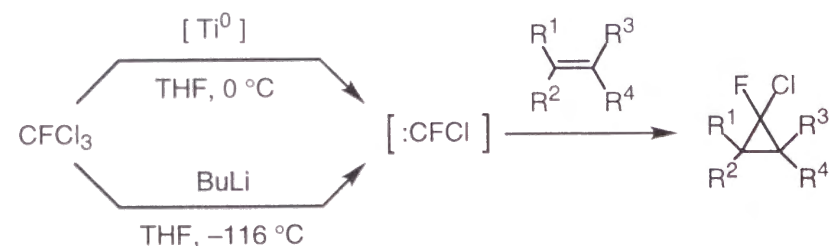
Inductive effect

*p*-*p* repulsion

Synthetic application of fluorocarbenes, the decomposition resultants of the corresponding carbenoid reagents, has precedents. Elsheimer and Dolbier reported that the fluorocarbene generated from diiodofluoromethane and diethylzinc at 94 °C reacted with olefin to 1,3-pentadiene the corresponding fluorovinylcyclopropanes.¹⁴⁾

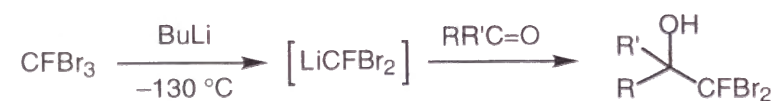


Likewise, upon reduction with low valent titanium at 0 °C in the presence of olefins, trichlorofluoromethane also gives chlorofluorocyclopropanes.¹⁵⁾ Burton and Hahnfeld reported that dichlorofluoromethyl lithium prepared from trichlorofluoromethane and butyllithium was labile at -116 °C to decompose, giving chlorofluorocarbene immediately.^{16d)} In contrast to these electrophilic carbene reactions, nucleophilic reactions of fluorine-substituted carbenoids have remained unexplored.



In view of the synthetic utility of fluorohalomethylmetal reagents that are readily available from polyhalofluoromethanes, the Author selected tribromofluoromethane (Fluorocarbon-11B3)¹⁶⁾ and studied the preparation and reactions of various fluoromethylmetal reagents that should be useful as a fluorine-substituted C₁ building block.

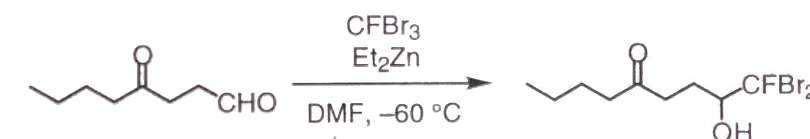
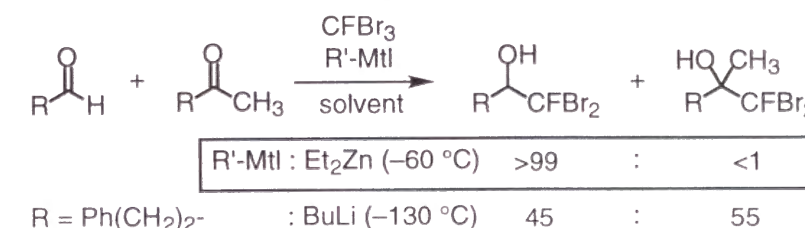
Although fluorohalomethylmetal reagents are thermally labile to hamper synthetic applications, the Author has disclosed that dibromofluoromethyl lithium^{16d)} can be generated by bromine-lithium exchange of tribromofluoromethane with butyllithium at -130 °C and react smoothly with a variety of aldehydes and ketones to give 1,1-dibromo-1-fluoro-2-alkanols.



Lithium carbenoid LiCFBr₂ was indeed found to be thermally unstable: all the reaction should be done at -130 °C. The Author planned to replace the lithium with zinc to find that the resulting zinc carbenoids were more stable. Indeed, treatment of tribromofluoromethane with diethylzinc¹⁷⁾ in DMF at -60 °C successfully generated the corresponding zinc carbenoid¹⁸⁾ which reacted with aldehydes to afford the dibromofluoro alcohols.

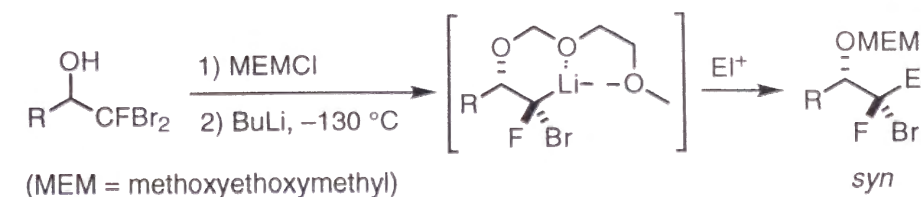


The chemoselectivity of the zinc carbenoid is worthy to note.¹⁹⁾ In a competition experiment with 3-phenylpropanal and 4-phenylbutan-2-one, the zinc carbenoid reacted with aldehyde preferentially. Dibromofluoromethyl lithium was shown to be non-selective. The high chemoselectivity is a striking feature of the zinc carbenoid. In a similar manner, an intramolecular chemoselective reaction is possible. Details are discussed in Chapter 2.

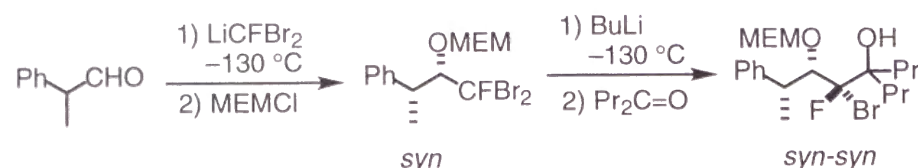


Control of the configuration of a fluorine-substituted nucleophilic center is one of the important issues in the synthesis of chiral organofluorine compounds.²⁰⁾ Chapter 3 describes a novel method for the selective construction of a -CFBr- moiety. Such stereochemical control methodology has no precedents.

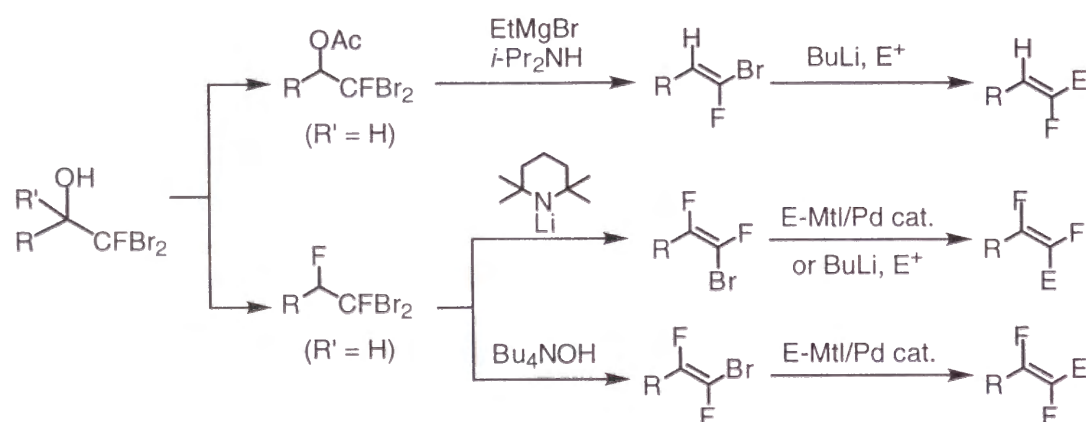
Treatment of RCH[OCH₂O(CH₂)₂OCH₃]CFBr₂, a MEM protected form of the alcohols obtained in Chapter 2, with butyllithium at -130 °C gives a lithium carbenoid diastereoselectively.²¹⁾ Exchange of *pro*-(*R*)-bromine-lithium is considered to proceed preferentially, and the resulting carbenoid undergoes reaction with an electrophile with retention of configuration to afford products of *syn* configuration selectively.



When this transformation is applied to the substrate derived from 2-phenylpropanal, a *syn-syn* alcohol is obtained highly selectively that has three contiguous stereocenters including a -CFBr- moiety.²²⁾



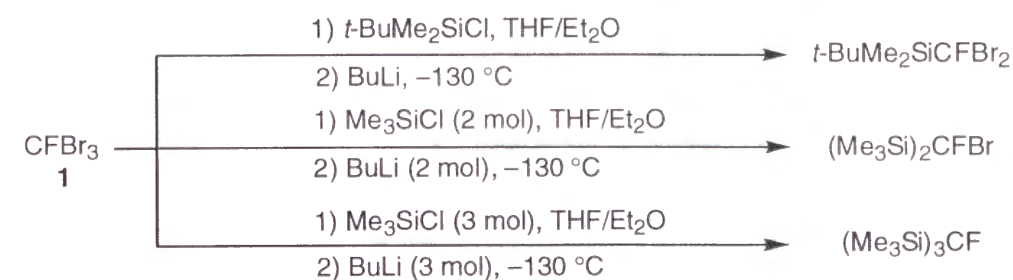
Described in Chapter 4 is the synthesis of stereoselective fluoro olefins.²³⁾ Fluoro olefins are important biological agents and functional materials. Especially, the structural moiety has attracted attention as an isostere of peptide bonds: irreversible activity is suggested based on the mechanism of an enzyme reaction. Alcohols obtained in Chapter 2 are converted into (*E*)-1-bromo-1-fluoro-1-alkenes²⁴⁾ stereoselectively by reductive elimination of the corresponding acetates. Fluorination the alcohol with DAST (Et_2NSF_3) followed by base treatment affords to (*E*) or (*Z*)-1-bromo-1,2-difluoro-1-alkenes stereoselectively depending on the counter ion of the base. The remaining bromine in the olefin products is converted into a carbonaceous substituent through metalation or cross-coupling reaction. The final transformation takes place with retention of configuration. Accordingly, the whole sequence of reactions allow us to construct monofluoro olefins and 1,2-difluoro olefins highly stereoselectively.



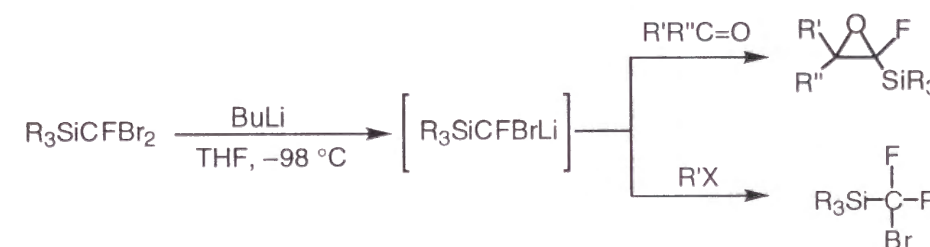
Chapter 5 deals with the chemistry of silicon-substituted fluoromethylmetal reagents.²⁵⁾ Since a silyl group has an α -anion stabilizing effect²⁶⁾ and serves as a clue for further transformation,²⁷⁾ the Author aimed to develop novel silyl- and fluorine-containing building blocks and examined the preparation of fluoropoly(organosilyl)-

methane.

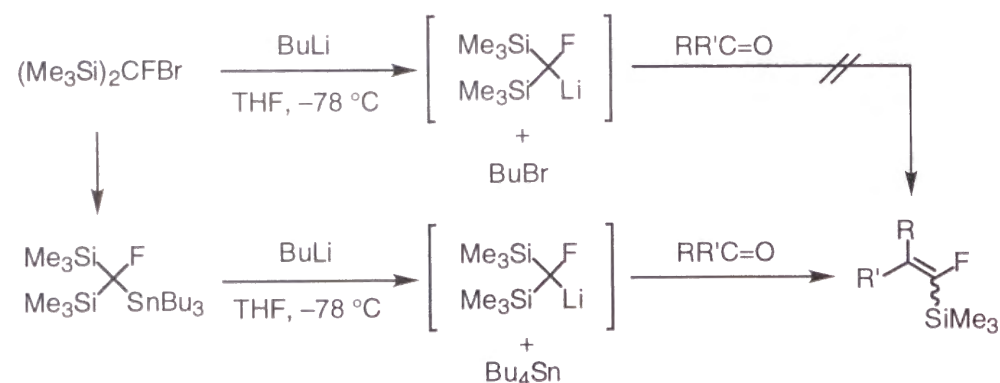
Treatment of tribromofluoromethane with 1 molar amount of butyllithium in the presence of 1 molar amounts of *t*-butyldimethylsilylchlorosilane gave *t*-Bu(Me)₂SiCFBr₂. Bis(trimethylsilyl)fluoromethane and tris(trimethylsilyl)fluoromethane were prepared using the corresponding amounts of chlorosilane and butyllithium.



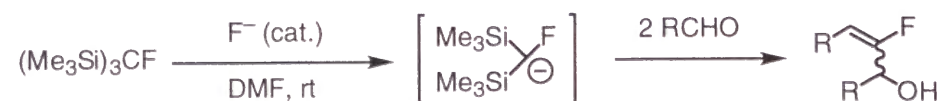
Treatment of the monosilylated dibromofluoromethane with butyllithium in THF at $-98\text{ }^\circ\text{C}$ gave a carbenoid reagent, which was allowed to react with aldehydes and ketones to give 1-fluoro-1-silyloxiranes. The bulky silyl group appears to accelerate the ring nucleophilic closure in spite of a retarding effect caused by fluorine. Alkylation of the silyl- and fluoro-substituted carbenoid was also achieved efficiently.



Because bis(organosilyl)methylmetal reagents afford alkenylsilane²⁸⁾ by the Peterson-olefination reaction, the Author first attempted to prepare the corresponding lithium reagent from bromofluorobis(trimethylsilyl)methane and butyllithium and react the reagent with carbonyl compounds to observe the expected 1-fluoroalkenylsilanes were not produced. Thus, he took an alternative tin-lithium exchange route and observed this route was effective for the synthesis of 1-fluoroalkenylsilanes.



Fluorotris(trimethylsilyl)methane, upon reaction with 2 mol amounts of an aromatic aldehyde and a catalytic amount of KF/18-crown-6, is found to give 1,3-disubstituted 2-fluoro-2-propen-1-ols.



In conclusion, the present Thesis describes the reactivity of fluoromethylmetal reagents derived from tribromofluoromethane. The sequence of transformations starting with tribromofluoromethane as a fluorine source allows us to obtain stereoselectively a wide variety of organofluorine compounds, which have been receiving growing interest in a broad area of medicinal, agricultural, and material sciences.

References

- 1) "Fusso Kagoubutsu no Gousei to Kinou," ed by N. Ishikawa and T. Kobayashi, Kodan-sha (1979).
- 2) Reviews on the organofluorine chemistry: a) "Fluorine-Containing Molecules. Structure, Reactivity, Synthesis, and Applications.," ed. by J. F. Liebman, A. Greenberg, and W. R. Dolbier, VCH, New York (1988); b) "Selective Fluorination in Organic and Bioorganic Chemistry," ed. by J. T. Welch, American Chemical Society, Washington, DC (1991); c) M. Hudlicky, "Chemistry of Organic Fluorine Compounds. 2nd (Revised) Edition," Ellis Horwood, New York (1992); d) "Organofluorine Chemistry. Principles and Commercial Applications," ed. by R. E. Banks, B. E. Smart, and J. C. Tatlow, Plenum Press, New York (1994); e) "Chemistry of Organic Fluorine Compounds II. A Critical Review," ed. by M. Hudlicky and A. E. Pavlath, American Chemical Society, Washington, DC (1995). For reviews on the synthesis of organofluorine compounds: f) J. T. Welch, *Tetrahedron*, **43**, 3123 (1987); g) P. Bravo and G. Resnati, *Tetrahedron: Asymmetry*, **1**, 661 (1990); h) J. A. Wilkinson, *Chem. Rev.*, **92**, 505 (1992); i) G. Resnati, *Tetrahedron*, **49**, 9385 (1993); j) J. M. Percy, *Contemporary Organic Synthesis*, **2**, 251 (1995); k) M. J. Tozer and T. F. Herpin, *Tetrahedron*, **52**, 8619 (1996).
- 3) "Fusso no Kagaku," ed. by T. Kitazume, T. Ishihara, and T. Taguchi, Kodan-sha (1993).
- 4) a) J. A. Wilkinson, *Chem. Rev.*, **92**, 505 (1992); b) K. Uneyama, *J. Syn. Org. Chem. Jpn.*, **51**, 70 (1993).
- 5) a) M. Kuroboshi and T. Hiyama, *Synlett*, **1991**, 909; b) M. Kuroboshi and T. Hiyama, *Chem. Lett.*, **1992**, 827.
- 6) a) T. Fuchikami, *Yuki Gosei Kagaku Kyokai Shi.*, **42**, 775 (1984); Takeuchi, Y. *Yuki Gosei Kagaku Kyokai Shi.*, **46**, 145 (1988).
- 7) a) G. Köbrich, K. Flory, and R. H. Fischer, *Chem. Ber.*, **99**, 1793 (1966); b) G. Köbrich, H. Trapp, K. Flory, and W. Driscel, *Chem. Ber.*, **99**, 689 (1966); c) G. Köbrich and H. R. Merkle, *Chem. Ber.*, **99**, 1782 (1966); d) J. Villieras, C. Bacquet, D. Masure, and J. F. Normant, *J. Organomet. Chem.*, **50**, C7 (1973); e) J. Villieras, C. Bacquet, and J. F. Normant, *Bull. Soc. Chim. Fr.* **1975**, 1797; f) J. Villieras, P. Perriot, and J. F. Normant, *Bull. Soc. Chim. Fr.*, **1977**, 765; g) J. Villieras, and M. Rambaud, *Synthesis*, **1980**, 644; h) J. Villieras, M. Rambaud, R. Tarhouni, and B. Kirschleger, *Synthesis*, **1981**, 68; i) G. Köbrich, and R. H. Fischer, *Tetrahedron*, **24**, 4343 (1968); j) J. Villieras, *J. Organomet. Chem. Rev. A*, **7**, 81 (1971); k) J. Villieras, M. Rambaud, R. Tarhouni, and B. Kirschleger,

- Synthesis*, **1981**, 68; l) T. Shono, H. Ohmizu, S. Kawakami, S. Nakano, and N. Kise, *Tetrahedron Lett.*, **22**, 871 (1981); m) T. Shono, H. Ohmizu, and N. Kise, *Tetrahedron Lett.*, **23**, 4801 (1982); n) T. Shono, N. Kise, and T. Suzumoto, *J. Am. Chem. Soc.*, **106**, 259 (1984); o) T. Tabuchi, J. Inanaga, and M. Yamaguchi, *Tetrahedron Lett.*, **27**, 3891 (1986); p) T. Imamoto, T. Takeyama, and H. Koto, *Tetrahedron Lett.*, **27**, 3243 (1986).
- 8) a) G. Cainelli, N. Tangari, and A. U. Ronchi, *Tetrahedron*, **28**, 3009 (1972); b) H. Taguchi, H. Yamamoto, and H. Nozaki, *Bull. Chem. Soc. Jpn.*, **50**, 1588 (1977); c) J. Villieras, *Bull. Soc. Chim. Fr.*, **1967**, 1511; d) J. Villieras, *Bull. Soc. Chim. Fr.*, **1967**, 1520; e) D. Seyferth, R. L. Lambert, and E. M. Jr. Hanason, *J. Organomet. Chem.*, **24**, 647 (1970).
- 9) a) H. Taguchi, H. Yamamoto, and H. Nozaki, *Tetrahedron Lett.*, **46**, 4661 (1972); b) H. Taguchi, S. Tanaka, H. Yamamoto, and H. Nozaki, *Tetrahedron Lett.*, **27**, 2465 (1975).
- 10) a) G. Köbrich and W. Werner, *Tetrahedron Lett.*, **26**, 2181 (1969); b) G. Köbrich, *Angew. Chem. Int. Ed. Engl.*, **11**, 473 (1972); c) J. Villieras, *J. Organomet. Chem.*, **40**, C1 (1972).
- 11) Fluorinated carbenoids with such an anion-stabilizing group as $(RO)_2PO-$, $PhSO-$, or $PhSO_2-$ are capable of nucleophilic reactions with carbonyl compounds and alkyl halides. D. J. Burton, Z.-Y. Yang, and W. Qiu, *Chem. Rev.*, **96**, 1641 (1996).
- 12) For a review on fluorinated carbenes, see a) D. L. S. Brahms and W. P. Dailey, *Chem. Rev.*, **96**, 1585 (1996).
- 13) "Fluorine in Organic Chemistry" ed. by R. D. Chambers, John Wiley & Sons. Inc., New York (1973).
- 14) S. Elsheimer and W. R. Jr. Dolbier, *J. Fluorine Chem.*, **40**, 119 (1988).
- 15) W. R. Jr. Dolbier and C. R. Burkholder, *J. Org. Chem.*, **55**, 589 (1990).
- 16) For syntheses of fluorinated compounds using tribromofluoromethane, see: a) R. W. Vanderhaar, D. J. Burton, and D. G. Nae, *J. Fluorine Chem.*, **1**, 381 (1972); b) J. P. Sloan, J. M. Tedder, and J. C. Walton, *J. Chem. Soc., Faraday Trans. 1*, **69**, 1143 (1973); c) D. J. Burton and R. M. Flynn, *J. Fluorine Chem.*, **10**, 329 (1977); d) D. J. Burton and J. L. Hahnfeld, *J. Org. Chem.*, **42**, 828 (1977); e) Y. Katsuhara and D. D. DesMarteau, *J. Am. Chem. Soc.*, **102**, 2681 (1980); f) D. J. Burton, S. Shin-Ya, and H. S. Kesling, *J. Fluorine Chem.*, **20**, 89 (1982); g) D. J. Burton, *J. Fluorine Chem.*, **23**, 339 (1983); h) D. J. Burton and D. M. Wiemers, *J. Fluorine Chem.*, **27**, 85 (1985); i) I. H. Jeong, D. J. Burton, and D. G. Cox, *Tetrahedron Lett.*, **27**, 3709 (1986); j) D. G. Cox and D. J. Burton, *J. Org. Chem.*,

- 53**, 366 (1988); k) D. Su, W. Cen, R. L. Kirchmeier, and J. M. Shreeve, *Can. J. Chem.*, **67**, 1795 (1989); l) H. Bürger and P. Moritz, *Organometallics*, **12**, 4930 (1993); m) C. Patois and P. Savignac, *J. Chem. Soc., Chem. Commun.*, 1993, 1711; n) C. Patois and P. Savignac, *Synth. Commun.*, **24**, 1317 (1994); o) J. Nieschalk and D. O'Hagan, *J. Chem. Soc., Chem. Commun.*, 1995, 719; p) J. Nieschalk, A. S. Batsanov, D. O'Hagan, and J. A. K. Howard, *Tetrahedron*, **52**, 165 (1996); q) R. Waschbusch, J. Carran, and P. Savignac, *Tetrahedron*, **52**, 14199 (1996).
- 17) For the pioneering work with diethylzinc as a reducing reagent, see: a) J. Furukawa, N. Kawabata, and J. Nishimura, *Tetrahedron Lett.*, **28**, 3353 (1966); b) J. Furukawa, N. Kawabata, and J. Nishimura, *Tetrahedron*, **24**, 53 (1968).
- 18) A recent review on zinc carbenoids: W. B. Motherwell and C. J. Nutley, *Contemporary Organic Synthesis*, **1**, 219 (1994).
- 19) Chemoselective carbonyl addition of organometallic reagents were carried out with B: a) H. C. Brown, U. R. Khire, G. Narla, and U. S. Racherla, *J. Org. Chem.*, **60**, 544 (1995). Mg: b) M. T. Reetz, N. Harmat, and R. Mahrwald, *Angew. Chem. Int. Ed. Engl.*, **31**, 342 (1992). Cr: c) Y. Okude, S. Hirano, T. Hiyama, and H. Nozaki, *J. Am. Chem. Soc.*, **99**, 3179 (1977); d) T. Hiyama, Y. Okude, K. Kimura, and H. Nozaki, *Bull. Chem. Soc. Jpn.*, **55**, 561 (1982); e) K. Takai, K. Kimura, T. Kuroda, T. Hiyama, and H. Nozaki, *Tetrahedron Lett.*, **24**, 5281 (1983); f) K. Takai, T. Kuroda, S. Nakatsukasa, K. Oshima, and H. Nozaki, *Tetrahedron Lett.*, **26**, 5585 (1985). Ti: g) M. T. Reetz, *Organotitanium Reagents in Organic Synthesis*; Springer-Verlag: Berlin, chapter 3 (1986); h) T. Kauffmann, T. Abel, W. Li, G. Neiteler, M. Schreer, and D. Schwarze, *Chem. Ber.*, **126**, 459 (1993). Cu: i) Y. Yamamoto, S. Yamamoto, H. Yatagai, Y. Ishihara, and K. Maruyama, *J. Org. Chem.*, **47**, 119 (1982). Zn: j) Y. Gao, H. Urabe, and F. Sato, *J. Org. Chem.*, **59**, 5521 (1994). Sn: k) A. Yanagisawa, H. Inoue, M. Morodome, and H. Yamamoto, *J. Am. Chem. Soc.*, **115**, 10356 (1993). Pb: l) Y. Yamamoto, and J.-i. Yamada, *J. Am. Chem. Soc.*, **109**, 4395 (1987). Bi: m) M. Wada, H. Ohki, and K.-y. Akiba, *Tetrahedron Lett.*, **27**, 4771 (1986). Zn/Ti and Zn/Al: n) T. Okazoe, J.-i. Hibino, K. Takai, and H. Nozaki, *Tetrahedron Lett.*, **26**, 5581 (1985).
- 20) a) "Biomedical Aspects of Fluorine Chemistry," ed. by R. Filler, and Y. Kobayashi, Kodansha Ltd. and Elsevier Biomedical Press: Tokyo and Amsterdam (1982); b) "Biomedical Frontiers of Fluorine Chemistry," ed. by I. Ojima, J. R. McCarthy, and J. T. Welch, American Chemical Society: Washington, D. C. (1996).

- 21) a) R. W. Hoffmann and M. Julius, *J. Organomet. Chem.*, **353**, C30 (1988); b) R. W. Hoffmann and M. Julius, *Liebigs Ann. Chem.*, **1991**, 811.
- 22) For a diastereoselective synthesis of α -bromo- α -fluoro- β -hydroxy ester, see K. Iseki, Y. Kuroki, and T. Kobayashi, *Tetrahedron Lett.*, **38**, 7209 (1997).
- 23) a) O. Yokokoji, T. Shimizu, and S. Kumai, JP 08040952 (1996); *Chem. Abstr.*, **124**, 316586 (1996); b) O. Yokokoji, T. Shimizu, and S. Kumai, JP 08059525 (1996); *Chem. Abstr.*, **125**, 45736 (1996); c) T. Shimizu, O. Yokokoji, and S. Kumai, JP 08119887 (1996); *Chem. Abstr.*, **125**, 128460 (1996); d) T. Allmendinger, E. Felder, and E. Hungerbuehler, in "Selective Fluorination in Organic and Bioorganic Chemistry," ed. by J. T. Welch, American Chemical Society, Washington, DC (1991), p 186; e) P. Bey, J. R. McCarthy, and I. A. McDolanld, in "Selective Fluorination in Organic and Bioorganic Chemistry," ed. by J. T. Welch, American Chemical Society, Washington, DC (1991), p 105.
- 24) For the synthesis of 1-bromo-1,2-difluoroethenes, see: a) R. N. Haszeldine, J. R. McAllister, and A. E. Tipping, *J. Chem. Soc., Perkin Trans. I*, **1974**, 1303; b) C. F. Smith, E. J. Soloski, and C. Tamborski, *J. Fluorine Chem.*, **4**, 35 (1974); c) R. D. Howells and H. Gilman, *J. Fluorine Chem.*, **4**, 247 (1974); d) R. D. Howells and H. Gilman, *J. Fluorine Chem.*, **5**, 99 (1975); e) N. Thoai, *J. Fluorine Chem.*, **5**, 115 (1975); f) P. Moreau, G. Dalverny, and A. Commeyras, *J. Chem. Soc., Chem. Commun.*, **1976**, 174; g) T. Fuchikami and I. Ojima, *J. Organomet. Chem.*, **212**, 145 (1981); h) T. Gouyon, R. Sauvetre, and J. F. Normant, *J. Organomet. Chem.*, **394**, 37 (1990); i) V. A. Petrov, C. G. Krespan, and B. E. Smart, *J. Fluorine Chem.*, **77**, 139 (1996). For 1-bromo-1-fluoro ethenes: j) R. E. Banks, M. G. Barlow, W. D. Davies, R. N. Haszeldine, K. Mullen, and D. R. Taylor, *Tetrahedron Lett.*, **1968**, 3909; k) R. E. Banks, M. G. Barlow, W. D. Davies, R. N. Haszeldine, and D. R. Taylor, *J. Chem. Soc. C*, **1969**, 1104; l) R. W. Vanderhaar, D. J. Burton, and D. G. Nae, *J. Fluorine Chem.*, **1**, 381 (1972); m) R. N. Haszeldine, I.-u. -D. Mir, and A. E. Tipping, *J. Chem. Soc., Perkin Trans. I*, **1976**, 2349; n) R. E. Banks, W. D. Davies, R. N. Haszeldine, and D. R. Taylor, *J. Fluorine Chem.*, **10**, 487 (1977); o) M. Shimizu, G.-H. Cheng, and H. Yoshioka, *J. Fluorine Chem.*, **41**, 425 (1988); p) S. Eddarir, C. Francesch, H. Mestdagh, and C. Rolando, *Tetrahedron Lett.*, **31**, 4449 (1990); q) J. Weber, L. Xu, and U. H. Brinker, *Tetrahedron Lett.*, **33**, 4537 (1992).
- 25) a) T. Hiyama, K. Nishide, and M. Obayashi, *Chem. Lett.*, **1984**, 1765; b) S. Martin, R. Sauvetre, and J.-F. Normant, *J. Organomet. Chem.*, **264**, 155 (1984); c) S. Martin, R. Sauvetre, and J.-F. Normant, *J. Organomet. Chem.*, **303**, 317 (1986); d) P. Martinet, R. Sauvetre, and J.-F. Normant, *Bull. Soc. Chim. Fr.*,

- 127**, 86 (1990); e) S. A. Fontana, C. R. Davis, Y.-B. He, and D. J. Burton, *Tetrahedron*, **52**, 37 (1996); f) L. Xue, L. Lu, S. D. P. Q. Liu, R. M. Narske, and D. J. Burton, *J. Org. Chem.*, **62**, 1064 (1997); g) F. Tellier, M. Audouin, M. Baudry, and R. Sauvetre, *Tetrahedron Lett.*, **39**, 5041 (1998).
- 26) a) A. R. Bassindale and P. G. Taylor, "The Chemistry of Organic Silicon Compounds," Vol. 2, ed. by S. Patai and Z. Rappoport, John Wiley & Sons, Inc., New York, 1989, pp. 893-963; b) J. S. Panek, "Comprehensive Organic Synthesis," Vol. 1, ed. by B. M. Trost and I. Fleming, Pergamon Press, London, 1991, pp. 579-627.
- 27) Preparations and reactions of dihalo(trialkylsilyl)methylolithiums: a) D. Seyferth, J. F. M. Armbricht, and E. M. Hanson, *J. Organomet. Chem.*, **10**, 25 (1967); b) D. Seyferth, J. R. L. Lambert, and E. M. Hanson, *J. Organomet. Chem.*, **24**, 647 (1970); c) D. Seyferth, E. M. Hanson, and J. F. M. Armbricht, *J. Organomet. Chem.*, **23**, 361 (1970); d) G. Köbrich and R. v. Nagel, *Tetrahedron Lett.*, **1970**, 4693; e) R. v. Nagel and G. Köbrich, *Tetrahedron Lett.*, **1970**, 4697; f) J. Villieras, C. Bacquet, D. Masure, and J. F. Normant, *J. Organomet. Chem.*, **50**, C7 (1973); g) J. Villieras, C. Bacquet, and J.-F. Normant, *Bull. Soc. Chim. Fr.*, **1975**, 1797; h) V. G. Fritz and U. Finke, *Z. Anorg. Allg. Chem.*, **430**, 121 (1977); i) G. L. Larson and O. Rosario, *J. Organomet. Chem.*, **168**, 13 (1979); j) A. Hosomi, M. Inaba, and H. Sakurai, *Tetrahedron Lett.*, **1983**, 4727; k) H. Shinokubo, K. Miura, K. Oshima, and K. Utimoto, *Tetrahedron Lett.*, **34**, 1951 (1993); l) H. Shinokubo, K. Oshima, and K. Utimoto, *Tetrahedron Lett.*, **35**, 3741 (1994); m) H. Shinokubo, K. Oshima, and K. Utimoto, *Chem. Lett.*, **1995**, 461; n) H. Shinokubo, K. Miura, K. Oshima, and K. Utimoto, *Tetrahedron*, **52**, 503 (1994); o) H. Shinokubo, K. Oshima, and K. Utimoto, *Tetrahedron*, **52**, 14533 (1996).
- 28) a) H. Sakurai, K.-i. Nishiwaki, and M. Kira, *Tetrahedron Lett.*, **1973**, 4193; b) B.-T. Grobel and D. Seebach, *Angew. Chem. Int. Ed. Engl.*, **13**, 83 (1974); c) B.-T. Grobel and D. Seebach, *Chem. Ber.*, **110**, 852 (1977); d) D. Seyferth, J. L. Lefferts, and J. R. L. Lambert, *J. Organomet. Chem.*, **142**, 39 (1977); e) I. Fleming and C. D. Floyd, *J. Chem. Soc., Perkin Trans. I*, **1981**, 969; f) D. J. Ager, *J. Org. Chem.*, **49**, 168 (1984); g) R. K. Boeckman, Jr., and R. L. Chinn, *Tetrahedron Lett.*, **26**, 5005 (1985); h) P. F. Hudrlik, E. L. O. Agwaramgbo, and A. M. Hudrlik, *J. Org. Chem.*, **54**, 5613 (1989); i) C. Palomo, J. M. Aizpurua, J. M. Garcia, I. Ganboa, F. P. Cossio, B. Lecea, and C. Lopez, *J. Org. Chem.*, **55**, 2498 (1990).

Abbreviations

bp	boiling point	rt	room temperature
brs	broad siglet	s	singlet
Bu	butyl	t	triplet
d	doublet	THF	tetrahydrofuran
DMF	<i>N,N</i> -dimethylforamide	TLC	thin layer chromatography
ed.	edition	TBAF	tetrabutylammonium fluoride
equiv.	equivalent		
Et	ethyl		
HMPA	hexamethylphosphoric triamide		
Hz	hertz (s^{-1})		
IR	infrared (spectrum)		
m	multiplet		
M	molar concentration (1 M = 1 mol dm ⁻³)		
Me	methyl		
mL	1 mL (1 cm ³)		
mmol	milimol		
mp	melting point		
NMR	nuclear magnetic resonance		
Ph	phenyl		
Pr	propyl		
q	quartet		
R _f	relative mobility		

Chapter 2

Generation and Carbonyl Addition of Lithium and Zinc Carbenoid Reagents Derived from Tribromofluoromethane

Treatment of tribromofluoromethane with butyllithium in a 2 : 1 mixture of THF and diethyl ether at $-130\text{ }^{\circ}\text{C}$ generated dibromofluoromethylithium which reacted smoothly with coexisting aldehydes or ketones ($\text{RR}'\text{C}=\text{O}$) to give fluorinated alcohols $\text{RR}'\text{C}(\text{OH})\text{CFBr}_2$. The corresponding zinc carbenoid reagent, EtZnCFBr_2 , was conveniently prepared by treatment of tribromofluoromethane with diethylzinc in DMF at $-60\text{ }^{\circ}\text{C}$ and reacted with aldehydes chemoselectively to give the dibromofluoro alcohols in higher yields.

2-1 Introduction

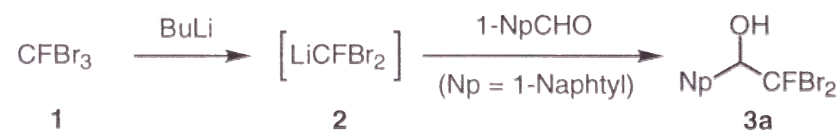
Carbenoids are highly versatile and widely used reagents in organic synthesis¹⁾ and are defined by Köbrich as compounds that have a metal atom and a leaving group on the same carbon. Fluorine-containing carbenoids are one of the most reliable reagents,²⁾ and indeed a variety of examples are prepared and applied to the synthesis of organofluorine compounds that have been recently attracting much attention in view of pharmaceutical, agrochemical, or material science.³⁾ Among the fluorine-containing carbenoids, fluorohalomethylmetals have a high potential as a C₁ synthetic unit, because the carbon-halogen bond(s) of the initial products can be converted into carbon-carbon bond(s) and/or various carbon-heteroatom bond(s). In general, however, fluorohalomethylmetals are thermally labile⁴⁾ and decompose readily to give electrophilic fluorocarbenes.⁵⁾ In contrast, nucleophilic reactions of the fluorine-substituted carbenoids remained unexplored.⁶⁾

2-2 Generation and Carbonyl Addition of Dibromofluoromethylithium

The Author has envisaged that tribromofluoromethane (**1**) would be a versatile precursor of monofluorinated carbenoid **2**, because **2** has a polyhalogenated functionality and **1** is commercially available. Indeed **1** was reported to be a useful starting material for the synthesis of monofluoro compounds.⁷⁾

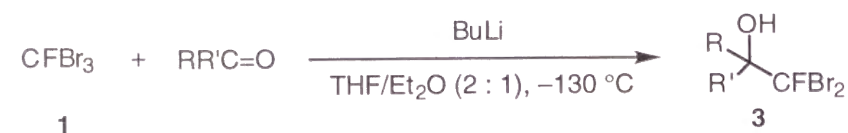
Using naphthalene-1-carbaldehyde as a typical electrophile, the Author first studied the generation and aldehyde addition of lithium carbenoid **2**. In fact, carbenoid **2** was successfully generated by treatment of **1** with an equimolar amount of butyllithium at -130 °C (Scheme 2-1). However, the carbenoid reagent proved to be extremely labile thermally, as demonstrated by treatment of **2** with the aldehyde *after* the carbenoid generation, giving adduct **3a** in only 10% yield. When the carbenoid generation was carried out *in the presence of* the aldehyde, **3a** was isolated in 85% yield. The same reaction carried out at -78 °C or 0 °C gave **3a** in 30% or 0% yield. Therefore, he concluded the procedure involving the carbenoid generation in the presence of an electrophile was essential particularly for carbenoid **2**.

Scheme 2-1. Generation and carbonyl addition of lithium carbenoid **2**.



The above procedure was applied to various aldehydes and ketones, and the results are summarized in Table 2-1. Both aromatic and aliphatic aldehydes gave **3** in good yields. Noteworthy is that ketones also are good substrates (Table 2-1, runs 12-15). α,β -Unsaturated carbonyl compounds gave the corresponding 1,2-adducts (Table 2-1, runs 10, 15) exclusively. Any butyl adducts, *n*-BuC(OH)RR', were not detected in all cases. Accordingly, at -130 °C, the bromine-lithium exchange appears to be faster than the carbonyl addition of butyllithium.

Another characteristic feature is that the Darzen-type reaction does not take place in contrast to LiCH₂Br or LiCHBr₂, which, upon warming a reaction mixture to room temperature, generally gives epoxides.⁸⁾ The lithium alkoxide of **3** did not cyclize even on heating at the refluxing temperature of THF. These observations accord with the fact that the fluorine-substituted carbon of **3** is reluctant to nucleophilic substitution reaction due probably to a shielding effect of a fluorine atom.⁹⁾

Table 2-1. Reaction of **1** with carbonyl compounds.^{a)}

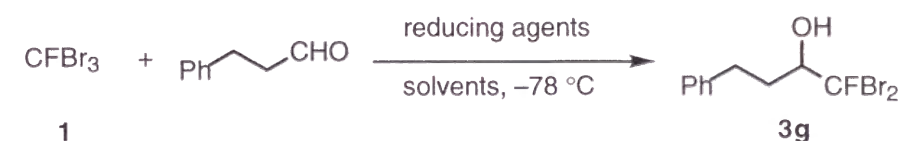
run	carbonyl compound		product	yield/% ^{b)}
	R	R'		
1	1-naphthyl-	H	3a	85
2	4-NC-C ₆ H ₄ -	H	3b	85
3	4-O ₂ N-C ₆ H ₄ -	H	3c	77
4	4-MeO-C ₆ H ₄ -	H	3d	87
5	3,4-(OCH ₂ O)-C ₆ H ₃ -	H	3e	90
6	Ph	H	3f	78
7	Ph(CH ₂) ₂ -	H	3g	81
8	c-Hex	H	3h	71
9	i-Pr	H	3i	56
10	trans-PhCH=CH-	H	3j	60 ^{c)}
11	n-C ₁₁ H ₂₃ -	H	3k	82
12	Ph	Ph	3l	64
13	Ph	Me	3m	96
14	-(CH ₂) ₅ -		3n	72
15	Me ₂ C=CH-	Me	3o	86

a) Butyllithium (1.0 mmol) was added to a solution of CFBr₃ (1.2 mmol) and a carbonyl compound (1 mmol) in THF-Et₂O (6 ml/3 ml) at -130 °C. b) Isolated yields. c) Dodecanal (1 mmol) and CFBr₃ (1.2 mmol) dissolved in THF-Et₂O (10 ml/5 ml) were allowed to react with butyllithium (1 mmol).

2-3-1 Generation and Aldehyde Addition of Zinc Carbenoid

As above, the lithium carbenoid generated by bromine-lithium exchange of tribromofluoromethane (**1**) with butyllithium reacted with aldehydes and ketones to give the corresponding adducts **3** in good yields. Since the lithium carbenoid is thermally unstable because of *p* orbitals repulsion (fluorine and lithium),¹⁰⁾ all operations need to be performed at -130 °C. The Author anticipated that a carbenoid with a proper counter metal would stabilize the anionic center.

At first, the Author examined metalation agents of tribromofluoromethane at -78 °C by trapping with 3-phenylpropanal. With isopropylmagnesium chloride, the yield of the corresponding alcohol was low (Table 2-2, runs 1-2). The alcohol was not produced with an aluminum reagent (Table 2-2, run 3). In contrast, zinc carbenoid¹¹⁾ was found to be satisfactory: treatment of tribromofluoromethane with diethylzinc¹²⁾ at -78 °C in THF-DMF gave the corresponding adduct, **3g**, in a moderate yield (Table 2-2, run 6).

Table 2-2. Reducing agents for tribromofluoromethane.^{a)}

run	reducing agent	solvent	yield/% ^{b)}
1	i-PrMgCl	Et ₂ O	13
2	i-PrMgCl	THF	39
3	Me ₃ Al	hexane	0
4	Et ₂ Zn	THF	0
5	Et ₂ Zn	THF-HMPA ^{c)}	37
6	Et ₂ Zn	THF-DMF ^{c)}	60

a) A reducing agent (1.5 mmol) was added into a solution of CFBr₃ (1.5 mmol) and 3-phenylpropanal (1 mmol) in a solvent (2 ml) at -78 °C. b) Isolated yields are given. c) HMPA or DMF (10 mmol) was used.

2-3-2 Solvent Effect

The Author next studied solvent effect in generation of the zinc carbenoid. In hexane, toluene, diethyl ether, or THF, the zinc carbenoid was not efficiently generated (Table 2-3, runs 1-4). Addition of such a polar solvent as HMPA or DMF to THF improved the yield of alcohol **3g** (Table 2-3, runs 8-9). The zinc carbenoid could be generated in DMF at $-60\text{ }^{\circ}\text{C}$ by treatment of tribromofluoromethane with diethylzinc and reacted with the aldehyde to afford **3g** in 87% yield (Table 2-3, run 10). Thus, the stability of zinc carbenoid was improved very much in DMF.¹³⁾

The same reaction carried out at $-40\text{ }^{\circ}\text{C}$ or $0\text{ }^{\circ}\text{C}$ gave **3g** in a lower or null yield (Table 2-3, runs 11-12).

Table 2-3. Solvent effect of zinc carbenoid.^{a)}

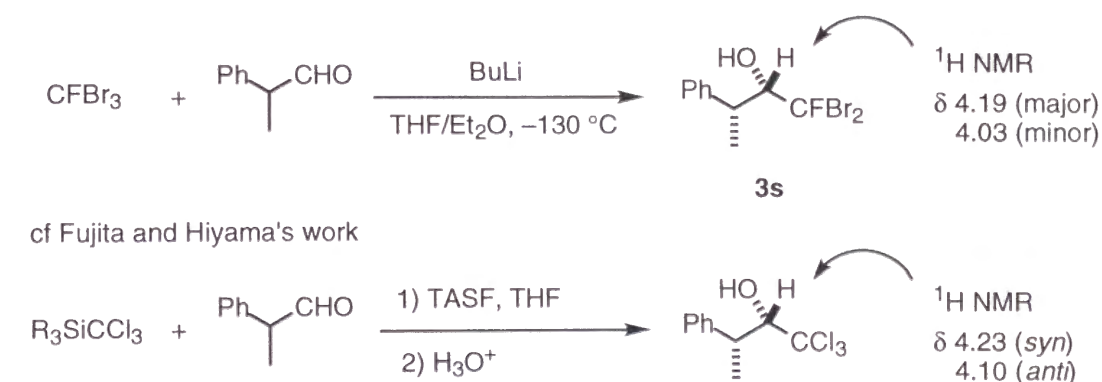
$\text{CFBr}_3 + \text{Ph-CH}_2\text{CH}_2\text{CHO} \xrightarrow[\text{solvent, temp.}]{\text{Et}_2\text{Zn}} \text{Ph-CH}_2\text{CH}_2\text{CH(OH)CFBr}_2$			
run	solvent	temp/ $^{\circ}\text{C}$	yield/% ^{b)}
1	hexane	$-78\text{ }^{\circ}\text{C}$	0
2	toluene	$-78\text{ }^{\circ}\text{C}$	0
3	Et_2O	$-78\text{ }^{\circ}\text{C}$	0
4	THF	$-78\text{ }^{\circ}\text{C}$	0
5	THF-DMSO ^{c)}	$-78\text{ }^{\circ}\text{C}$	trace
6	THF-DMPU ^{c)}	$-78\text{ }^{\circ}\text{C}$	trace
7	THF- CH_3CN ^{c)}	$-78\text{ }^{\circ}\text{C}$	0
8	THF-HMPA ^{c)}	$-78\text{ }^{\circ}\text{C}$	37
9	THF-DMF ^{c)}	$-78\text{ }^{\circ}\text{C}$	60
10	DMF	$-60\text{ }^{\circ}\text{C}$	87
11	DMF	$-40\text{ }^{\circ}\text{C}$	51
12	DMF	$0\text{ }^{\circ}\text{C}$	0

a) Diethylzinc (1.5 mmol) was added to a solution of CFBr_3 (1.5 mmol) and 3-phenylpropanal (1 mmol) in the above listed solvent (2 ml) at $-78\text{ }^{\circ}\text{C}$.

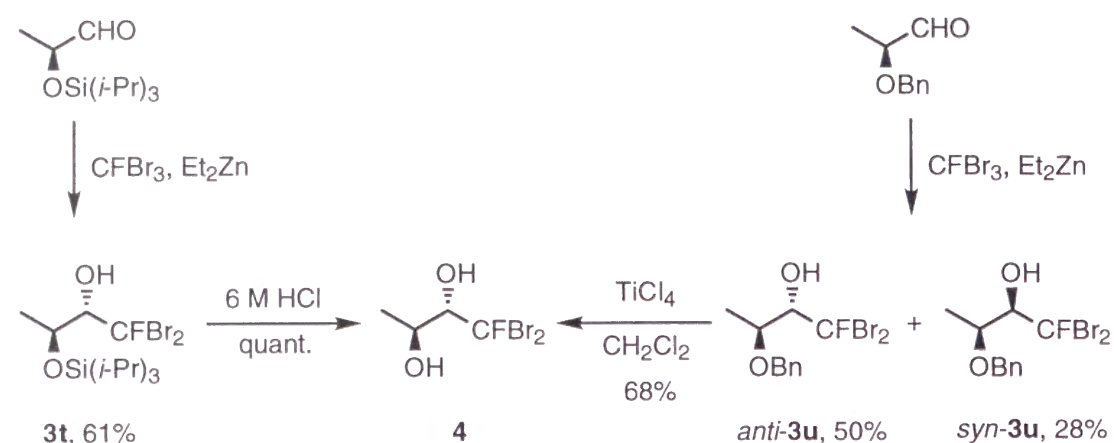
b) Isolated yields. c) DMSO, DMPU, CH_3CN , HMPA, or DMF (10 mmol) was used.

The above-mentioned procedure was applied to various aldehydes as summarized in Table 2-4. Naphthalene-1-carbaldehyde and benzaldehyde gave the corresponding alcohols **3a** and **3f** in moderate yields (Table 2-4, runs 1, 4). While an aldehyde having an electron-withdrawing group (nitro group) gave product **3c** in a high yield (Table 2-4, run 2), that with an electron-donating group gave product **3d** less efficiently (Table 2-4, run 3). Cinnamaldehyde did not give the corresponding alcohol **3k** (Table 2-4, run 8). 1-Phenylpropanal, 1-phenylethanal, and octanal gave the desired products, **3g**, **3q**, and **3r**, in good yields (Table 2-4, runs 5, 10-11). In cases of 2-methylpropanal and cyclohexanecarbaldehyde, low yields of products resulted (Table 2-4, runs 6-7). 2-Phenylpropanal gave alcohol **3s** in 52% yield with high *syn* selectivity (Table 2-4, run 12). The stereochemistry of **3s** was assigned by comparison of the ^1H NMR chemical shift with 1,1,1-trichloro-3-phenyl-2-butanol¹⁴⁾ and based on Cram's rule.¹⁵⁾

Scheme 2-2. Assignment of the stereochemistry of **3s** from ^1H NMR chemical shift.



In case of (*S*)-2-(triisopropylsiloxy)propanal,¹⁶⁾ the stereochemistry of product **3t** was shown to be *anti* (Table 2-4, run 13). The stereochemistry of **3t** was determined by conversion to the corresponding diol **4** by desilylation using hydrogen chloride. Meanwhile, zinc carbenoid reacted with (*S*)-2-benzyloxypropanal to afford a mixture of *anti* **3u** and *syn* **3u** products (Table 2-4, run 14, Scheme 2-3). The stereochemistry of the *anti* product **3u** was determined by X-ray analysis. The *anti* product **3u** was converted titanium tetrachloride to diol **4**, identical to the diol obtained from **3t** (Scheme 2-3). The selectivity can be understood in terms of the Felkin-Anh model.¹⁷⁾

Scheme 2-3. Determination of stereochemistry of **3t**.

The reaction of the same aldehyde with lithium carbenoid **2** gives **3t** (*syn* : *anti* = 74 : 26, 59% yield). The high selectivity attained with the zinc carbenoid reagent is remarkable. 2,2-Dimethylpropanal having a quaternary carbon next to the formyl group did not react with the zinc carbenoid (Table 2-4, run 15).

Table 2-4. Reaction of zinc carbenoid with aldehyde.

$\text{CFBr}_3 \quad + \quad \text{RCHO} \quad \xrightarrow[\text{DMF, } -60^\circ\text{C to rt}]{\text{Et}_2\text{Zn}} \quad \text{R}-\text{CH}(\text{OH})-\text{CFBr}_2$			
1			
run	RCHO	product	yield/% ^{a)}
1	1-Naphthyl-	3a	48
2	4-NO ₂ -C ₆ H ₄ -	3c	93
3	4-MeO-C ₆ H ₄ -	3d	10 ^{b)}
4	Ph-	3f	48
5	Ph(CH ₂) ₂ -	3g	87
6	<i>n</i> -C ₆ H ₁₁ -	3h	47
7	(CH ₃) ₂ CH-	3i	53
8	(<i>E</i>)-PhCH=CH-	3k	trace
9	4-AcO-C ₆ H ₄ -	3p	52
10	PhCH ₂ -	3q	69
11	CH ₃ (CH ₂) ₆ -	3r	69
12	Ph(CH ₃)CH-	3s	52 ^{c)}
13	(<i>S</i>)-CH ₃ [OSi(<i>i</i> -Pr) ₃]CH-	3t	61 ^{d)}
14	(<i>S</i>)-CH ₃ (OBn)CH-	3u	78 ^{e)}
15	(CH ₃) ₃ C-	3v	0

a) Isolated yields. b) The yield was determined by ¹H NMR using 1,1,2-trichloroethene as an internal standard. c) *syn* : *anti* = 95 : 5. d) *syn* : *anti* = <5 : >95. e) *syn* : *anti* = 36 : 64.

2-3-3 Salt Effect

As discussed above, the carbonyl addition of the zinc carbenoid derived from tribromofluoromethane (**1**) was influenced by the steric and electronic environment of substrates. Villieras and his co-workers observed the presence of a lithium salt improved the stability of lithium carbenoids and attributed the improved stability to an intermolecular halogen-lithium interaction, weakening an intramolecular halogen-lithium interaction.¹⁸⁾

Based on their observation, the Author studied effect of a lithium salt in the generation and reaction of the zinc carbenoid using benzaldehyde as an electrophile. First, he screened some lithium halides in the reaction at $-60\text{ }^{\circ}\text{C}$ and found that some were effective in improvement of yields; lithium chloride was the best (Table 2-5, runs 2-5). The zinc carbenoid reagent gave fluorinated alcohol **3f** in 75%, 71%, or 66% at $-50\text{ }^{\circ}\text{C}$, $-40\text{ }^{\circ}\text{C}$, or $-30\text{ }^{\circ}\text{C}$, respectively, (Table 2-5, runs 7-9) but in 12% yield at $0\text{ }^{\circ}\text{C}$. Similar improvement was observed with cyclohexanecarbaldehyde (66% yield). However, 4-methoxybenzaldehyde did not give higher yields of product.

Table 2-5. Effect of lithium salts.^{a)}

$\text{CFBr}_3 + \text{PhCHO} + \text{LiX} \xrightarrow[\text{DMF}]{\text{Et}_2\text{Zn}}$			
$\text{Ph}-\text{CH}(\text{OH})-\text{CFBr}_2$			
run	temp/ $^{\circ}\text{C}$	salt	yield/% ^{b)}
1	-60	none	48
2	-60	LiF	73
3	-60	LiCl	78
4	-60	LiBr	45
5	-60	LiI	60
6	-60	LiCl	78
7	-50	LiCl	75
8	-42	LiCl	71
9	-30	LiCl	66
10	0	LiCl	12

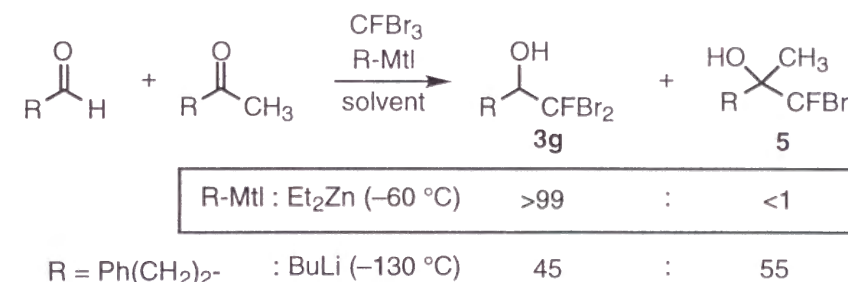
a) aldehyde : CFBr_3 : LiX : Et_2Zn = 1 : 1.3 : 1.8 : 1.3.

b) Isolated yields.

2-4 Chemoselective Carbonyl Addition

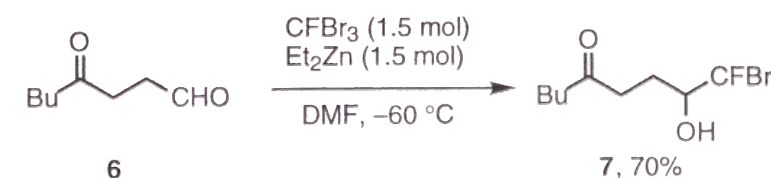
The Author next studied the reaction of the zinc carbenoid with ketone substrate 4-phenylbutan-2-one, but the desired adduct was not produced. Thus, the reactivity of zinc carbenoid appears to be much lower than that of lithium carbenoid and suggests a possibility of chemoselective addition reaction to an aldehyde in the presence of a ketone.¹⁹⁾ Indeed, in a competition experiment using 3-phenylpropanal (1 mol) and 4-phenylbutan-2-one (1 mol), the zinc carbenoid (1.5 mol) prepared as above reacted with 1-phenylpropanal selectively to give **3g** in 85% yield with ketone adduct **5** in less than 1% yield (Scheme 2-4). In contrast, the reaction of lithium carbenoid **2** gave a mixture of the adducts (**3g** : **5** = 45 : 55).

Scheme 2-4. Intermolecular reaction of zinc carbenoid.



Furthermore, an intramolecular chemoselective reaction is possible. Thus, the reaction of keto aldehyde **6** with the zinc carbenoid gave aldehyde adduct **7** as a sole product (Scheme 2-5).

Scheme 2-5. Intramolecular reaction of zinc carbenoid.



2-5 Summary

The Author has demonstrated that dibromofluoromethylithium (**2**) is generated from tribromofluoromethane (**1**) successfully at $-130\text{ }^{\circ}\text{C}$ to react with aldehydes or ketones, giving 2-substituted 1,1-dibromo-1-fluoro-2-alkanols (**3**) in good yields. The Author have also shown that the corresponding zinc carbenoid can be generated using diethylzinc in lieu of butyllithium in DMF at $-60\text{ }^{\circ}\text{C}$ and successively reacts with aldehydes chemoselectively. Use of a lithium salt improved the yields of the corresponding adducts.

2-6 Experimental Section

General

Following instrumentation applies to the whole experimental parts of this Thesis. All temperatures were uncorrected. The melting points were determined using an Olympus polarization microscope (BH-2) equipped with a Mettler hot stage (FP-90, FP-82). ^1H NMR spectra were measured on a Bruker AC 200 (200 MHz), JEOL JNM-GX 270 (270 MHz), or JNM-FX 100 (100 MHz) spectrometer. Chemical shifts of ^1H NMR are expressed in parts per million downfield relative to an internal tetramethylsilane ($\delta = 0\text{ ppm}$) or chloroform ($\delta = 7.26\text{ ppm}$). Splitting patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; brs, broad singlet. ^{13}C NMR spectra were measured on a Bruker AC 200 (50 MHz) spectrometer with tetramethylsilane as an internal standard ($\delta = 0\text{ ppm}$). ^{19}F NMR spectra were measured on a Bruker AC 200 (188 MHz) or JEOL JNM-FX 100 (94 MHz) spectrometer with trichlorofluoromethane as an internal standard ($\delta = 0\text{ ppm}$). Chemical-shift values are given in parts per million downfield relative to the internal standard. Infrared spectra (IR) were recorded on a Hitachi 260-10 or Shimadzu FTIR-8100A spectrometer. GC-MS analyses were performed, unless otherwise noted, with a Shimadzu GC-MS QP-5000 or Hitachi M-80 spectrometer by electron ionization at 70 eV. High-resolution mass spectra were obtained with a JEOL JMS-700 spectrometer. Elemental analyses were carried out with a YANAKO MT2 CHN CORDER machine. TLC analyses were performed by means of Merck Kieselgel 60 F_{254} and column chromatography was carried out using Merck Kieselgel 60 (230-400 mesh). Capillary gas chromatography was performed with a Shimadzu GC-17A chromatograph equipped with a DB-1 column (0.25 mm x 30 m). Preparative HPLC was carried out with an LC-908 chromatograph (Japan Analytical Industry Co., Ltd.) using a JAIGEL-1H or 2H GPC column. THF, diethyl ether, 1,4-dioxane, and hexane were distilled from benzophenone and sodium before use under a nitrogen atmosphere. Dichloromethane and DMF were distilled from calcium hydride prior to use under a nitrogen atmosphere. Tribromofluoromethane was purchased from PCR or Aldrich Chemical Company, Inc., and used without further purification. Butyllithium was purchased from Kanto Chemical Co., Inc. and titrated before use with anhydrous 2-butanol with 1,10-phenanthroline as an indicator. Chlorotrimethylsilane and *t*-butylchlorodimethylsilane were kindly donated by Shin-Etsu Chemical Co. Ltd., Japan. All reactions were carried out under an argon atmosphere. Cooling a reaction vessel at $-130\text{ }^{\circ}\text{C}$ was effected using a mixture of liquid nitrogen and pentane.

General Procedure for Generation and Carbonyl Addition of Dibromofluoromethylithium

To a solution of tribromofluoromethane (**1**) (59 μ l, 0.60 mmol) and an aldehyde or ketone (0.50 mmol) in THF (3 ml)–Et₂O (1.5 ml) was added a 1.60 M hexane solution of butyllithium (3.1 ml, 0.50 mmol) at –130 °C via a syringe over a period of 10 min. The resulting mixture was stirred for 0.5 h at –130 °C before quenching with a sat. NH₄Cl aq. solution. The aq. layer was extracted with diethyl ether (20 ml x 5). The combined extracts were dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by silica-gel column chromatography to afford fluorinated alcohol **3**.

General Procedure for Generation and Aldehyde Addition of zinc Carbenoid

A 1.0 M hexane solution of diethyl zinc (1.5 ml, 1.50 mmol) was added dropwise to a solution of tribromofluoromethane (**1**) (0.147 ml, 1.50 mmol) and an aldehyde (1.00 mmol) in DMF (3 ml) at –60 °C via a syringe over a period of 10 min. The resulting mixture was stirred for 3 h at –130 °C before quenching with a sat. NH₄Cl aq. solution. The aq. layer was extracted with diethyl ether (20 ml x 5). Workup and purification as above gave **3**.

2,2-Dibromo-2-fluoro-1-(1-naphthyl)ethanol (3a): Obtained in 85% yield as a yellow oil, *R_f* 0.30 (hexane–ethyl acetate = 5 : 1). ¹H NMR (200 MHz, CDCl₃) δ = 3.19 (d, *J* = 3.4 Hz, 1H), 6.02 (dd, *J* = 2.7, 8.1 Hz, 1H), 7.42–7.66 (m, 3H), 7.85–8.13 (m, 4H); ¹³C NMR (50 MHz, CDCl₃) δ = 78.5 (d, *J* = 22.6 Hz), 103.0 (d, *J* = 326.3 Hz), 123.5 (d, *J* = 3.1 Hz), 125.1, 125.8, 126.7, 127.0, 129.1, 130.3, 131.2, 131.6, 133.7; ¹⁹F NMR (188 MHz, CDCl₃) δ = –60.3 (d, *J* = 8.1 Hz); IR (neat) 3425, 3050, 1510, 1395, 1350, 1260, 1230, 1205, 1170, 1095, 1080, 1030, 1010, 980, 920, 865, 815 cm^{–1}; MS *m/z* (rel intensity) 351 (*M*⁺+5, 0.5), 350 (*M*⁺+4, 4), 349 (*M*⁺+3, 1), 348 (*M*⁺+2, 8), 347 (*M*⁺+1, 0.6), 346 (*M*⁺, 4), 157 (100), 129 (64). Found: C, 41.61; H, 2.78%. Calcd for C₁₂H₉Br₂FO: C, 41.42; H, 2.61%.

2,2-Dibromo-1-(4-cyanophenyl)-2-fluoroethanol (3b): Isolated in 85% yield as colorless plates, mp 122–123 °C. ¹H NMR (200 MHz, CDCl₃) δ = 3.60 (brs, 1H), 5.18 (d, *J* = 8.3 Hz, 1H), 7.68 (s, 4H); ¹³C NMR (50 MHz, CDCl₃) δ = 82.0 (d, *J* = 22.5 Hz), 101.5 (d, *J* = 323.6 Hz), 113.1, 118.4, 129.5, 131.9, 140.0; ¹⁹F NMR (188 MHz, CDCl₃) δ = –62.8 (d, *J* = 8.3 Hz); IR (CH₂Cl₂) 3390, 9050, 2220, 1400, 1290, 1230, 1190, 1080, 1005, 995, 870, 850, 835, 798, 780 cm^{–1}; MS *m/z* (rel

intensity) 325 (*M*⁺+4, 0.1), 323 (*M*⁺+2, 0.2), 321 (*M*⁺, 0.1), 132 (100), 104 (28). Found: C, 33.56; H, 1.90; N, 4.34%. Calcd for C₉H₆Br₂FNO: C, 33.47; H, 1.87; N, 4.34%.

2,2-Dibromo-2-fluoro-1-(4-nitrophenyl)ethanol (3c): This compound was obtained in 77% yield as a colorless powder, mp 122–123 °C. ¹H NMR (200 MHz, CDCl₃) δ = 3.43 (brs, 1H), 5.25 (d, *J* = 8.2 Hz, 1H), 7.76 (ddd, *J* = 0.5, 1.3, 9.0 Hz, 2H), 8.22–8.27 (m, 2H); ¹³C NMR (50 MHz, CDCl₃) δ = 81.9 (d, *J* = 22.6 Hz), 101.4 (d, *J* = 323.4 Hz), 123.2, 129.7 (d, *J* = 1.9 Hz), 141.6, 148.5; ¹⁹F NMR (188 MHz, CDCl₃) δ = –63.0 (d, *J* = 8.2 Hz); IR (KBr) 3380, 1510, 1340, 1075, 1255, 790, 690 cm^{–1}; MS *m/z* (rel intensity) 343 (*M*⁺+2, 30), 342 (*M*⁺+1, 14), 341 (*M*⁺, 34), 278 (28), 259 (59), 256 (70), 233 (29), 219 (15), 172 (38), 152 (48), 140 (34), 91 (60), 69 (100). Found: C, 28.35; H, 1.68%. Calcd for C₈H₆Br₂FNO₃: C, 28.02; H, 1.76%.

2,2-Dibromo-2-fluoro-1-(4-methoxyphenyl)ethanol (3d): Prepared in 87% yield as a colorless oil, *R_f* 0.40 (hexane–dichloromethane = 1 : 2). ¹H NMR (200 MHz, CDCl₃) δ = 3.18 (brs, 1H), 3.82 (s, 3H), 5.00 (d, *J* = 9.4 Hz, 1H), 6.88–6.95 (m, 2H), 7.44–7.49 (m, 2H); ¹³C NMR (50 MHz, CDCl₃) δ = 55.4, 82.7 (d, *J* = 22.2 Hz), 103.4 (d, *J* = 324.0 Hz), 113.6, 127.1, 129.9, 160.4; ¹⁹F NMR (188 MHz, CDCl₃) δ = –62.1 (d, *J* = 9.4 Hz); IR (neat) 3440, 1605, 1580, 1510, 1460, 1440, 1305, 1250, 1175, 1115, 1075, 1025, 990, 860, 830, 790, 705 cm^{–1}; MS *m/z* (rel intensity) 331 (*M*⁺+5, 0.2), 330 (*M*⁺+4, 1), 329 (*M*⁺+3, 0.3), 328 (*M*⁺+2, 3), 327 (*M*⁺+1, 0.2), 326 (*M*⁺, 1), 137 (10), 109 (25). Found: C, 32.68; H, 2.45%. Calcd for C₉H₉Br₂FO₂: C, 32.95; H, 2.76%.

2,2-Dibromo-2-fluoro-1-(3,4-methylenedioxyphenyl)ethanol (3e): This product was isolated in 90% yield as a colorless oil, *R_f* 0.50 (dichloromethane). ¹H NMR (200 MHz, CDCl₃) δ = 3.24 (brs, 1H), 5.02 (d, *J* = 9.4 Hz, 1H), 5.98 (s, 2H), 6.81 (d, *J* = 8.0 Hz, 1H), 6.97–7.05 (m, 2H); ¹³C NMR (50 MHz, CDCl₃) δ = 82.7 (d, *J* = 22.2 Hz), 101.4, 102.9 (d, *J* = 323.9 Hz), 107.9, 108.8, 122.9, 128.7, 147.5, 148.5; ¹⁹F NMR (188 MHz, CDCl₃) δ = –62.1 (d, *J* = 9.4 Hz); IR (neat) 3475, 2880, 1495, 1480, 1440, 1380, 1360, 1240, 1090, 1070, 1030, 990, 920, 895, 860, 825, 795, 735, 700 cm^{–1}; MS *m/z* (rel intensity) 345 (*M*⁺+5, 0.7), 344 (*M*⁺+4, 6), 343 (*M*⁺+3, 1.2), 342 (*M*⁺+2, 12), 341 (*M*⁺+1, 0.7), 340 (*M*⁺, 7), 182 (21), 151 (100). Found: C, 31.57; H, 2.01%. Calcd for C₉H₇Br₂FO₃: C, 31.61; H, 2.06%.

2,2-Dibromo-2-fluoro-1-phenylethanol (3f): This alcohol was produced in 78% yield as a colorless oil, *R_f* 0.61 (hexane–ethyl acetate = 5 : 1). ¹H NMR (200 MHz, CDCl₃) δ = 3.11 (brs, 1H), 5.12 (d, *J* = 9.4 Hz, 1H), 7.30–7.65 (m, 5H); ¹³C NMR (50 MHz, CDCl₃) δ = 82.7 (d, *J* = 22.0 Hz), 102.4 (d, *J* = 321.8 Hz), 128.0,

128.5 (d, $J = 1.9$ Hz), 129.3, 134.8; ^{19}F NMR (188 MHz, CDCl_3) $\delta = -62.3$ (d, $J = 9.4$ Hz); IR (neat) 3450, 3070, 3034, 1700, 1495, 1455, 1380, 1090, 1067, 1030, 994, 851, 804, 777, 733 cm^{-1} . Found: C, 32.01; H, 2.50%. Calcd for $\text{C}_8\text{H}_7\text{Br}_2\text{FO}$: C, 32.25; H, 2.37%.

1,1-Dibromo-1-fluoro-4-phenyl-2-butanol (3g): This alcohol was isolated in 81% yield as a colorless oil, R_f 0.45 (hexane–dichloromethane = 1 : 3). ^1H NMR (270 MHz, CDCl_3) $\delta = 1.87$ – 2.01 (m, 1H), 2.20 – 2.32 (m, 1H), 2.56 (d, $J = 5.3$ Hz, 1H), 2.77 (ddd, $J = 8.4, 8.4, 13.8$ Hz, 1H), 2.98 (ddd, $J = 4.8, 9.1, 14.0$ Hz, 1H), 3.86 (dddd, $J = 2.3, 5.6, 7.7, 12.8$ Hz, 1H), 7.19 – 7.36 (m, 5H); ^{13}C NMR (50 MHz, CDCl_3) $\delta = 31.6, 33.7, 80.5$ (d, $J = 21.1$ Hz), 104.2 (d, $J = 322.4$ Hz), $126.5, 128.7, 128.8, 140.8$; ^{19}F NMR (94 MHz, CDCl_3) $\delta = -60.1$ (d, $J = 7.7$ Hz); IR (neat) 3415, 3025, 2935, 15.5, 1460, 1105, 1085, 1055, 1020, 985, 830, 800, 750, 705 cm^{-1} ; MS m/z (rel intensity) 328 ($\text{M}^+ + 4$, 2), 327 ($\text{M}^+ + 3$, 3, 13), 326 ($\text{M}^+ + 2$, 4), 325 ($\text{M}^+ + 1$, 26), 324 (M^+ , 2), 323 ($\text{M}^+ - 1$, 13), 243 (10), 245 (10), 165 (100). Found: C, 36.70; H, 3.55%. Calcd for $\text{C}_{10}\text{H}_{11}\text{Br}_2\text{FO}$: C, 36.84; H, 3.40%.

2,2-Dibromo-2-fluoro-1-cyclohexylethanol (3h): The adduct was obtained in 71% yield as a colorless oil, R_f 0.40 (hexane–ethyl acetate = 8 : 1). ^1H NMR (200 MHz, CDCl_3) $\delta = 0.88$ – 1.43 (m, 5H), 1.60 – 2.02 (m, 6H), 2.58 (brs, 1H), 3.70 (dd, $J = 4.2, 11.2$ Hz, 1H); ^{13}C NMR (50 MHz, CDCl_3) $\delta = 25.9, 26.1, 26.2, 27.4, 30.8$ (d, $J = 2.8$ Hz), $40.6, 84.6$ (d, $J = 20.1$ Hz), 104.8 (d, $J = 327.7$ Hz); ^{19}F NMR (188 MHz, CDCl_3) $\delta = -57.4$ (d, $J = 11.2$ Hz); IR (neat) 3420, 2930, 2850, 1455, 1105, 1095, 1065, 1015, 900, 803, 745 cm^{-1} ; MS m/z (rel intensity) 207 (0.2), 205 (0.2), 142 (2), 141 (13), 95 (100), 55 (5). Found: C, 31.79; H, 4.36%. Calcd for $\text{C}_8\text{H}_{13}\text{Br}_2\text{FO}$: C, 31.61; H, 4.31%.

1,1-Dibromo-1-fluoro-3-methyl-2-butanol (3i): The product was isolated in 56% yield as a colorless oil, R_f 0.29 (hexane–ethyl acetate = 10 : 1). ^1H NMR (200 MHz, CDCl_3) $\delta = 1.07$ (d, $J = 2.5$ Hz, 3H), 1.10 (d, $J = 2.5$ Hz, 3H), 2.32 (m, 1H), 2.53 (d, $J = 6.2$ Hz, 1H), 3.72 (ddd, $J = 4.7, 6.2, 11.7$ Hz, 1H); ^{13}C NMR (50 MHz, CDCl_3) $\delta = 17.2$ (d, $J = 2.3$ Hz), 20.8 (d, $J = 3.8$ Hz), $30.9, 85.0$ (d, $J = 20.1$ Hz), 104.6 (d, $J = 326.0$ Hz); ^{19}F NMR (188 MHz, CDCl_3) $\delta = -58.1$ (d, $J = 11.7$ Hz); IR (neat) 3450, 2969, 2878, 2361, 2342, 1472, 1395, 1372, 1294, 1240, 1177, 1148, 1096, 1067, 1026, 968, 905, 851, 820, 799, 743 cm^{-1} ; MS m/z (rel intensity) 266 ($\text{M}^+ + 4$, 0.3), 264 ($\text{M}^+ + 2$, 0.7), 262 (M^+ , 0.2), 219 (6), 211 (3), 183 (3), 167 (12), 140 (39), 73 (100). HRMS Found: m/z 261.8984. Calcd for $\text{C}_5\text{H}_9\text{Br}_2\text{FO}$: M 261.9004.

(E)-1,1-Dibromo-1-fluoro-4-phenyl-3-buten-2-ol (3j): Produced in 82% yield as a colorless oil, R_f 0.40 (dichloromethane). ^1H NMR (100 MHz, CDCl_3) $\delta =$

2.95 (brs, 1H), 4.66 (dd, $J = 6.0, 6.6$ Hz, 1H), 6.25 (dd, $J = 6.0, 15.9$ Hz, 1H), 6.89 (d, $J = 15.9$ Hz, 1H), 7.28 – 7.48 (m, 5H); ^{13}C NMR (50 MHz, CDCl_3) $\delta = 81.8$ (d, $J = 22.5$ Hz), 102.6 (d, $J = 323.0$ Hz), $122.9, 127.0, 128.75, 128.82, 135.7, 136.5$; ^{19}F NMR (94 MHz, CDCl_3) $\delta = -61.0$ (d, $J = 6.6$ Hz); IR (neat) 3380, 1605, 1490, 1445, 1120, 1080, 990, 960, 830, 785, 735 cm^{-1} ; MS m/z (rel intensity) 327 ($\text{M}^+ + 5$, 0.2), 326 ($\text{M}^+ + 4$, 1), 325 ($\text{M}^+ + 3$, 0.3), 324 ($\text{M}^+ + 2$, 2), 323 ($\text{M}^+ + 1$, 0.1), 322 (M^+ , 1), 191 (3.6), 133 (100), 115 (41). Found: C, 37.45; H, 2.73%. Calcd for $\text{C}_{10}\text{H}_9\text{Br}_2\text{FO}$: C, 37.07; H, 2.80%.

1,1-Dibromo-1-fluoro-2-tridecanol (3k): Isolated in 60% yield as a colorless oil, R_f 0.45 (hexane–ethyl acetate = 5 : 1). ^1H NMR (270 MHz, CDCl_3) $\delta = 0.88$ (t, $J = 6.8$ Hz, 3H), 1.27 – 1.37 (m, 17H), 1.52 – 1.64 (m, 2H), 1.86 – 1.94 (m, 1H), 2.46 (dt, $J = 1.8, 7.4$ Hz, 1H), 3.83 – 3.92 (m, 1H); ^{13}C NMR (50 MHz, CDCl_3) $\delta = 14.1, 22.7, 25.6, 29.3, 29.4, 29.5, 29.57, 29.64, 31.9, 32.1$ (d, $J = 0.9$ Hz), 81.4 (d, $J = 21.1$ Hz), 104.5 (d, $J = 322.7$ Hz); ^{19}F NMR (94 MHz, CDCl_3) $\delta = -59.7$ (d, $J = 7.3$ Hz); IR (neat) 3390, 2930, 2860, 1475, 1385, 1315, 1100, 1035, 800, 770 cm^{-1} ; MS m/z (rel intensity) 185 (36), 121 (10), 69 (60), 43 (100). Found: C, 41.28; H, 6.43%. Calcd for $\text{C}_{13}\text{H}_{25}\text{Br}_2\text{FO}$: C, 41.51; H, 6.69%.

2,2-Dibromo-2-fluoro-1,1-diphenylethanol (3l): This product was obtained in 64% yield as colorless needles, mp 111–113 °C. ^1H NMR (100 MHz, CDCl_3) $\delta = 3.42$ (s, 1H), 7.22 – 7.34 (m, 10H); ^{13}C NMR (50 MHz, CDCl_3) $\delta = 85.0$ (d, $J = 18.4$ Hz), 108.6 (d, $J = 334.5$ Hz), 127.7 (d, $J = 3.4$ Hz), $128.0, 128.3, 140.3$ (d, $J = 1.7$ Hz); ^{19}F NMR (94 MHz, CDCl_3) $\delta = -57.0$; IR (KBr) 3545, 3057, 2361, 1541, 1491, 1448, 1327, 1300, 1190, 1153, 1089, 1057, 1034, 1010, 997, 933, 902, 756, 733, 700, 694, 655, 623, 617 cm^{-1} ; MS m/z (rel intensity) 376 ($\text{M}^+ + 4$, 0.1), 374 ($\text{M}^+ + 2$, 0.2), 372 (M^+ , 0.1), 183 (100), 165 (12), 105 (73). Found: C, 44.99; H, 2.83%. Calcd for $\text{C}_{14}\text{H}_{11}\text{Br}_2\text{FO}$: C, 44.96; H, 2.96%.

1,1-Dibromo-1-fluoro-2-phenyl-2-propanol (3m): This was produced in 96% yield as a colorless oil, R_f 0.40 (hexane–dichloromethane = 1 : 2). ^1H NMR (100 MHz, CDCl_3) $\delta = 1.94$ (d, $J = 1.2$ Hz, 3H), 2.82 (brs, 1H), 7.33 – 7.44 (m, 3H), 7.58 – 7.69 (m, 2H); ^{13}C NMR (50 MHz, CDCl_3) $\delta = 26.0, 81.9$ (d, $J = 19.5$ Hz), 109.2 (d, $J = 329.7$ Hz), $127.4, 127.9, 128.5, 138.9$; ^{19}F NMR (94 MHz, CDCl_3) $\delta = -59.6$ (d, $J = 1.2$ Hz); IR (neat) 3550, 1450, 1380, 1180, 1140, 1110, 1060, 1030, 950, 915, 805, 790, 730, 700 cm^{-1} ; MS m/z (rel intensity) 314 ($\text{M}^+ + 4$, 0.2), 312 ($\text{M}^+ + 2$, 0.3), 310 (M^+ , 0.2), 191 (15), 121 (100). Found: C, 34.36; H, 3.03%. Calcd for $\text{C}_9\text{H}_9\text{Br}_2\text{FO}$: C, 34.64; H, 2.91%.

1-(Dibromofluoromethyl)cyclohexanol (3n): This tertiary alcohol was

obtained in 72% yield as colorless needles, mp 47–48 °C. ^1H NMR (100 MHz, CDCl_3) δ = 1.26–2.01 (m, 11H); ^{13}C NMR (50 MHz, CDCl_3) δ = 21.7, 25.1, 31.7 (d, J = 1.1 Hz), 80.0 (d, J = 18.8 Hz), 111.8 (d, J = 328.3 Hz); ^{19}F NMR (94 MHz, CDCl_3) δ = –62.9; IR (KBr) 3480, 2941, 2858, 1450, 1160, 1140, 1107, 1041, 995, 956, 931, 810, 750 cm^{-1} ; MS m/z (rel intensity) 193 ($\text{M}^+ + 2 - \text{C}_6\text{H}_{11}\text{O}$, 1), 191 ($\text{M}^+ - \text{C}_6\text{H}_{11}\text{O}$, 3), 99 ($\text{M}^+ - \text{CFBr}_2$, 100). Found: C, 28.91; H, 3.76%. Calcd for $\text{C}_7\text{H}_{11}\text{Br}_2\text{FO}$: C, 29.00; H, 3.82%.

1,1-Dibromo-1-fluoro-2,4-dimethyl-3-penten-2-ol (3o): Obtained in 86% yield as a colorless oil, R_f 0.25 (hexane–ethyl acetate = 15 : 1). ^1H NMR (100 MHz, CDCl_3) δ = 1.64 (d, J = 1.0 Hz, 3H), 1.79 (d, J = 1.2 Hz, 3H), 1.93 (d, J = 1.5 Hz, 3H), 2.41 (s, 1H), 5.54 (d, J = 0.7 Hz, 1H); ^{13}C NMR (50 MHz, CDCl_3) δ = 19.2 (d, J = 0.6 Hz), 23.8 (d, J = 1.4 Hz), 27.6, 81.6 (d, J = 19.0 Hz), 110.1 (d, J = 330.2 Hz), 123.2 (d, J = 1.3 Hz); ^{19}F NMR (94 MHz, CDCl_3) δ = –62.9; IR (neat) 3560, 3460, 2980, 2930, 1670, 1450, 1385, 1330, 1225, 1130, 1070, 948, 851, 808, 770, 730 cm^{-1} ; MS (10 eV) m/z (rel intensity) 274 (0.4), 272 (0.3), 192 (2.7), 190 (5.2), 188 (2.9), 129 (4), 99 (100), 43 (98). Found: C, 29.15; H, 3.90%. Calcd for $\text{C}_7\text{H}_{11}\text{Br}_2\text{FO}$: C, 29.00; H, 3.82%.

2,2-Dibromo-2-fluoro-1-(4-acethoxyphenyl)ethanol (3p): Isolated in 52% yield as a white solid, R_f 0.39 (dichloromethane). ^1H NMR (200 MHz, CDCl_3) δ = 2.30 (s, 3H), 3.17 (brs, 1H), 5.11 (d, J = 9.2 Hz, 1H), 7.09–7.18 (m, 2H), 7.57 (brd, J = 8.2 Hz, 2H); ^{13}C NMR (50 MHz, CDCl_3) δ = 21.1, 82.4 (d, J = 22.0 Hz), 102.6 (d, J = 321.8 Hz), 112.2, 126.7, 129.7, 132.3, 169.2; ^{19}F NMR (188 MHz, CDCl_3) δ = –62.5 (d, J = 9.2 Hz); IR (neat) 3400, 1740, 1607, 1509, 1408, 1366, 1258, 1231, 1198, 1165, 1119, 1084, 1019, 997, 955, 939, 922, 864, 855, 795, 768, 708, 666, 640, 592, 573 523, 503 cm^{-1} . MS m/z (rel intensity) 358 ($\text{M}^+ + 4$, 8), 356 ($\text{M}^+ + 2$, 17), 354 (M^+ , 9), 123 (100). HRMS Found: m/z 353.8879. Calcd for $\text{C}_5\text{H}_9\text{Br}_2\text{FO}$: M 353.8902.

1,1-Dibromo-1-fluoro-3-phenyl-2-propanol (3q): This ketone adduct was isolated in 69% yield as a colorless oil, R_f 0.40 (hexane–ethyl acetate = 5 : 1). ^1H NMR (200 MHz, CDCl_3) δ = 2.60 (brs, 1H), 2.83 (dd, J = 9.8, 14.1 Hz, 1H), 3.28 (d, J = 14.1 Hz, 1H), 4.05–4.20 (m, 1H), 7.10–7.45 (m, 5H); ^{13}C NMR (50 MHz, CDCl_3) δ = 38.5 (d, J = 1.5 Hz), 82.1 (d, J = 21.6 Hz), 103.0 (d, J = 320.3 Hz), 127.0, 128.6, 129.4, 136.3; ^{19}F NMR (188 MHz, CDCl_3) δ = –60.7; IR (neat) 3520, 3450, 3088, 3065, 3031, 2934, 1719, 1603, 1497, 1455, 1437, 1383, 1273, 1181, 1094, 1032, 934, 912, 874, 843, 826, 789, 754, 720, 700, 629, 569 cm^{-1} . Found: C, 34.50; H, 2.90%. Calcd for $\text{C}_9\text{H}_9\text{Br}_2\text{FO}$: C, 34.65; H, 2.91%.

1,1-Dibromo-1-fluoro-2-nonanol (3r): This was isolated in 69% yield as a colorless oil, R_f 0.73 (hexane–dichloromethane = 1 : 3). ^1H NMR (200 MHz, CDCl_3) δ = 0.89 (t, J = 11.1 Hz, 3H), 1.10–2.00 (m, 12H), 2.46 (d, J = 6.1 Hz, 1H), 3.80–3.95 (m, 1H); ^{13}C NMR (50 MHz, CDCl_3) δ = 14.1, 22.6, 25.5, 29.1, 29.2, 31.7, 32.1 (d, J = 1.1 Hz), 81.4 (d, J = 21.4 Hz), 104.4 (d, J = 322.2 Hz); ^{19}F NMR (188 MHz, CDCl_3) δ = –59.7 (d, J = 6.8 Hz); IR (neat) 3400, 2957, 2928, 2857, 1466, 1379, 1136, 1086, 1046, 1024, 797, 762, 723 cm^{-1} . Found: C, 33.88; H, 5.18%. Calcd for $\text{C}_7\text{H}_{11}\text{Br}_2\text{FO}$: C, 33.78; H, 5.35%.

1,1-Dibromo-1-fluoro-3-phenyl-2-butanol (3s): This was obtained in 52% yield as a 95 : 5 mixture of *syn*- and *anti*-isomers. A pale yellow oil, R_f 0.44 (hexane–ethyl acetate = 5 : 1). ^1H NMR (200 MHz, CDCl_3) *syn*-isomer: δ = 1.43 (dd, J = 1.2, 7.0 Hz, 3H), 2.73 (d, J = 5.8 Hz, 1H), 3.47 (dq, J = 4.3, 7.0 Hz, 1H), 4.14 (ddd, J = 4.3, 5.9, 12.2 Hz, 1H), 7.22–7.32 (m, 5H), *anti*-isomer: δ = 4.03 (m, 1H); ^{13}C NMR (50 MHz, CDCl_3) *syn*-isomer: δ = 16.2 (d, J = 2.3 Hz), 41.6, 84.6 (d, J = 19.1 Hz), 104.0 (d, J = 329.6 Hz), 127.0, 127.8, 128.8, 144.2 (d, J = 1.2 Hz); ^{19}F NMR (188 MHz, CDCl_3) *syn*-isomer: δ = –58.8 (d, J = 12.2 Hz), *anti*-isomer: δ = –57.2; IR (neat) 3464, 3086, 3063, 3028, 2984, 2937, 1603, 1495, 1454, 1385, 1325, 1271, 1234, 1122, 1084, 1024, 1005, 991, 939, 850, 789, 765, 700 cm^{-1} ; MS m/z (rel intensity) 328 ($\text{M}^+ + 4$, 4), 326 ($\text{M}^+ + 2$, 7), 324 (M^+ , 4), 246 (5), 244 (5), 166 (14), 135 (27), 117 (22), 105 (100), 78 (89). Found: C, 36.66; H, 3.37%. Calcd for $\text{C}_{10}\text{H}_{11}\text{Br}_2\text{FO}$: C, 36.84; H, 3.40 %.

(2S, 3S)-1,1-Dibromo-1-fluoro-3-triisopropylsiloxy-2-butanol (3t):

This adduct was isolated in 61% yield as a colorless oil, R_f 0.65 (hexane–ethyl acetate = 4 : 1), $[\alpha]_D = -4.2^\circ$ (c = 1.22, MeOH). The diastereomeric ratio of *syn*- and *anti*- was > 95 : < 5. ^1H NMR (200 MHz, CDCl_3) δ = 1.00–1.22 (m, 21H), 1.30 (dd, J = 2.7, 6.3 Hz, 1H), 3.06 (d, J = 3.3 Hz, 1H), 4.15 (ddd, J = 3.3, 3.3, 16.2 Hz, 1H), 4.56 (dddd, J = 3.3, 6.3, 12.6, 12.6 Hz, 1H); ^{13}C NMR (50 MHz, CDCl_3) δ = 12.4, 17.6 (d, J = 4.0 Hz), 18.0 (d, J = 2.9 Hz), 68.7, 83.5 (d, J = 18.8 Hz), 97.8 (d, J = 326.2 Hz); ^{19}F NMR (94 MHz, CDCl_3) δ = –62.1 (d, J = 16.2 Hz); IR (neat) 3500, 2946, 2869, 1464, 1387, 1248, 1146, 1107, 1071, 1017, 980, 941, 884, 837, 787, 772, 681 cm^{-1} . Found: C, 6.57; H, 37.11%. Calcd for $\text{C}_7\text{H}_{11}\text{Br}_2\text{FO}$: C, 6.45; H, 36.98%.

(2S, 3S)-1,1-Dibromo-1-fluoro-3-benzyloxy-2-butanol (3u): Obtained in 50% yield as a colorless oil, mp = 69–70 °C, $[\alpha]_D = -3.5^\circ$ (c = 1.07, MeOH). ^1H NMR (200 MHz, CDCl_3) δ = 1.00–1.22 (m, 21H), 1.30 (dd, J = 2.7, 6.3 Hz, 1H), 3.06 (d, J = 3.3 Hz, 1H), 4.15 (ddd, J = 3.3, 3.3, 16.2 Hz, 1H), 4.56 (dddd, J = 3.3, 6.3, 12.6, 12.6 Hz, 1H); ^{13}C NMR (50 MHz, CDCl_3) δ = 12.4, 17.6 (d, J = 4.0 Hz), 18.0 (d, J =

2.9 Hz), 68.7, 83.5 (d, $J = 18.8$ Hz), 97.8 (d, $J = 326.2$ Hz); ^{19}F NMR (94 MHz, CDCl_3) $\delta = -62.1$ (d, $J = 16.2$ Hz); IR (neat) 3500, 2946, 2869, 1464, 1387, 1248, 1146, 1107, 1071, 1017, 980, 941, 884, 837, 787, 772, 681 cm^{-1} . Found: C, 36.81; H, 3.93%. Calcd for $\text{C}_7\text{H}_{11}\text{Br}_2\text{FO}$: C, 37.11; H, 3.68%. (2*R*, 3*S*)-isomer was isolated in 28% yield as a colorless oil, R_f 0.39 (hexane–ethyl acetate = 4 : 1), $[\alpha]_D = -0.7^\circ$ ($c = 1.30$, MeOH). ^1H NMR (200 MHz, CDCl_3) $\delta = 1.00$ – 1.22 (m, 21H), 1.30 (dd, $J = 2.7, 6.3$ Hz, 1H), 3.06 (d, $J = 3.3$ Hz, 1H), 4.15 (ddd, $J = 3.3, 3.3, 16.2$ Hz, 1H), 4.56 (dddd, $J = 3.3, 6.3, 12.6, 12.6$ Hz, 1H); ^{13}C NMR (50 MHz, CDCl_3) $\delta = 12.4, 17.6$ (d, $J = 4.0$ Hz), 18.0 (d, $J = 2.9$ Hz), 68.7, 83.5 (d, $J = 18.8$ Hz), 97.8 (d, $J = 326.2$ Hz); ^{19}F NMR (94 MHz, CDCl_3) $\delta = -62.1$ (d, $J = 16.2$ Hz); IR (neat) 3500, 2946, 2869, 1464, 1387, 1248, 1146, 1107, 1071, 1017, 980, 941, 884, 837, 787, 772, 681 cm^{-1} . Found: C, 37.24; H, 3.70%. Calcd for $\text{C}_7\text{H}_{11}\text{Br}_2\text{FO}$: C, 37.11; H, 3.68%.

(2*S*, 3*S*)-1,1-Dibromo-1-fluoro-2,3-butan-diol (4)

To a solution of (2*S*, 3*S*)-**3u** in dichloromethane (1 ml) was added TiCl_4 (31 μl) dropwise at room temperature under an argon atmosphere. The resulting mixture was stirred for 1 h at room temperature before quenching with a sat. NaHCO_3 aq. solution and neutralization with 1 M HCl solution. The aq. layer was extracted with diethyl ether (20 ml x 2). The combined extracts were dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by silica-gel column chromatography to afford diol **4** in 68% yield as a white solid, mp = 55–56 $^\circ\text{C}$, $[\alpha]_D = -3.5^\circ$ ($c = 0.34$, MeOH). ^1H NMR (200 MHz, CDCl_3) $\delta = 1.37$ (d, $J = 6.3$ Hz, 3H), 1.98 (brs, 1H), 2.90 (brs, 1H), 4.03 (ddd, $J = 5.1, 5.1, 11.4$ Hz, 1H), 4.29 (m, 1H); ^{13}C NMR (50 MHz, CDCl_3) $\delta = 18.1, 98.2, 83.2$ (d, $J = 19.5$ Hz), 100.3 (d, $J = 330.2$ Hz); ^{19}F NMR (188 MHz, CDCl_3) $\delta = -60.3$; IR (neat) 3450, 3250, 1290, 1120, 1090, 1000, 950, 910, 840, 780 cm^{-1} ; MS m/z (rel intensity) 253 ($\text{M}^+ - \text{Me} + 4$, 0.5), 251 ($\text{M}^+ - \text{Me} + 2$, 0.7), 249 ($\text{M}^+ - \text{Me}$, 0.4), 142 (97), 140 (100). HRMS Found: m/z 248.8586. Calcd for $\text{C}_3\text{H}_4\text{Br}_2\text{FO}_2$: M 248.8562.

1,1-Dibromo-1-fluoro-5-oxo-2-nonanol (7): The adduct was isolated in 70% yield as a colorless oil, R_f 0.61 (hexane–ethyl acetate = 2 : 1). ^1H NMR (200 MHz, CDCl_3) $\delta = 0.91$ (t, $J = 7.0$ Hz, 3H), 1.20–1.45 (m, 2H), 1.45–1.70 (m, 2H), 1.75–2.05 (m, 2H), 2.10–2.35 (m, 1H), 2.46 (t, $J = 7.2$ Hz, 1H), 2.65–2.80 (m, 2H), 2.32 (brs, 1H), 3.85–4.00 (m, 1H); ^{13}C NMR (50 MHz, CDCl_3) $\delta = 13.8, 22.3, 25.9$ (d, $J = 1.5$ Hz), 38.2, 42.3, 80.7 (d, $J = 21.2$ Hz), 103.5 (d, $J = 320.3$ Hz), 211.5; ^{19}F

NMR (188 MHz, CDCl_3) $\delta = -60.2$; IR (neat) 3428, 2959, 2934, 2874, 1707, 1466, 1410, 1379, 1312, 1262, 1117, 1084, 1040, 905, 789, 767, 766 cm^{-1} ; MS (70 eV). Found: C, 32.54; H, 4.66%. Calcd for $\text{C}_9\text{H}_{15}\text{Br}_2\text{FO}_2$: C, 32.54; H, 4.55%.

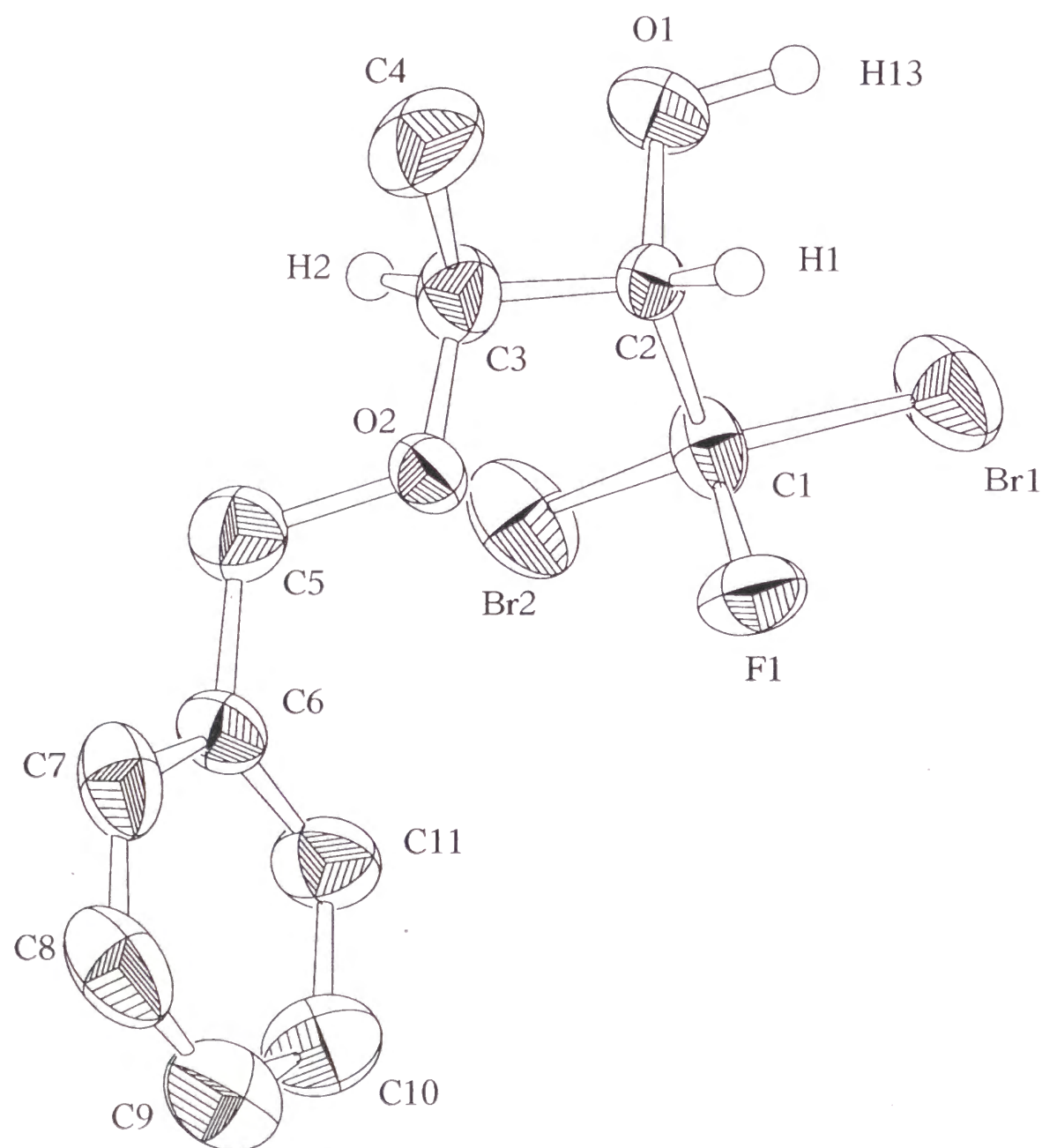


Fig. 1. ORTEP drawing of *anti*-**3u**

Data Collection

A colorless prismatic crystal of $C_{11}H_{13}O_2Br_2F$ having approximate dimensions of 0.40 x 0.20 x 0.15 mm was mounted on a glass fiber. All measurements were made on a Rigaku AFC5S diffractometer with graphite monochromated Mo-K α radiation.

Cell constants and an orientation matrix for data collection, obtained from a least-squares refinement using the setting angles of 25 carefully centered reflections in the range $20.25 < 2\theta < 24.66^\circ$ corresponded to a primitive orthorhombic cell with dimensions:

$$a = 10.205(2) \text{ \AA}$$

$$b = 13.237(3) \text{ \AA}$$

$$c = 9.538(2) \text{ \AA}$$

$$V = 1288.4(3) \text{ \AA}^3$$

For $Z = 4$ and F.W. = 356.03, the calculated density is 1.84 g/cm^3 . The systematic absences of:

$$\text{h00: } h \neq 2n$$

$$0k0: k \neq 2n$$

001: $1 \neq 2n$

uniquely determine the space group to be:

P2₁2₁2₁ (#19)

The data were collected at a temperature of $23 \pm 1^\circ\text{C}$ using the ω - 2θ scan technique to a maximum 2θ value of 55.0° . Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.12° with a take-off angle of 6.0° . Scans of $(1.10 + 0.50 \tan \theta)^\circ$ were made at a speed of $8.0^\circ/\text{min}$ (in omega). The weak reflections ($I < 10.0\sigma(I)$) were rescanned (maximum of 5 scans) and the counts were accumulated to ensure good counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting time to background counting time was 2:1. The diameter of the incident beam collimator was 1.0 mm, the crystal to detector distance was 258 mm, and the detector aperture was 9.0×13.0 mm (horizontal x vertical).

Data Reduction

A total of 1724 reflections was collected. The intensities of three representative reflection were measured after every 150 reflections. No decay correction was applied.

The linear absorption coefficient, μ , for Mo-K α radiation is 63.1 cm⁻¹. An empirical absorption correction based on azimuthal scans of several reflections was applied which resulted in transmission factors ranging from 0.53 to 1.00. The data were corrected for Lorentz and polarization effects.

Structure Solution and Refinement

The structure was solved by heavy-atom Patterson methods¹ and expanded using Fourier techniques². The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement³ was based on 850 observed reflections ($I > 3.00\sigma(I)$) and 145 variable parameters and converged (largest parameter was 0.00 times its esd) with unweighted and weighted agreement factors of:

$$R = \Sigma ||Fo| - |Fc|| / \Sigma |Fo| = 0.038$$

$$R_w = \sqrt{(\Sigma w(|Fo| - |Fc|)^2 / \Sigma w Fo^2)} = 0.025$$

The standard deviation of an observation of unit weight⁴ was 1.85. The weighting scheme was based on counting statistics and included a factor ($p = 0.002$) to downweight the intense reflections. Plots of $\Sigma w(|Fo| - |Fc|)^2$ versus $|Fo|$, reflection order in data collection, $\sin \theta / \lambda$ and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.53 and $-0.39 \text{ e}^-/\text{\AA}^3$, respectively.

Neutral atom scattering factors were taken from Cromer and Waber⁵. Anomalous dispersion effects were included in Fcalc⁶; the values for $\Delta f'$ and $\Delta f''$ were those of Creagh and McAuley⁷. The values for the mass attenuation coefficients are those of Creagh and Hubbel⁸. All calculations were performed using the teXsan⁹ crystallographic software package of Molecular Structure Corporation.

References

(1) PATY: Beurskens, P.T., Admiraal, G., Beurskens, G., Bosman, W.P., Garcia-Granda, S., Gould, R.O., Smits, J.M.M. and Smykalla, C. (1992). The DIRDIF program system, Technical Report of the Crystallography Laboratory, University of Nijmegen, The Netherlands.

(2) DIRDIF92: Beurskens, P.T., Admiraal, G., Beurskens, G., Bosman, W.P., Garcia-Granda, S., Gould, R.O., Smits, J.M.M. and Smykalla, C. (1992). The DIRDIF program system, Technical Report of the Crystallography Laboratory, University of Nijmegen, The Netherlands.

(3) Least-Squares:

Function minimized: $\Sigma w(|Fo| - |Fc|)^2$

$$\text{where } w = \frac{1}{\sigma^2(Fo)} = \frac{4Fo^2}{\sigma^2(Fo^2)}$$

$$\sigma^2(Fo^2) = \frac{S^2(C + R^2B) + (pFo^2)^2}{Lp^2}$$

S = Scan rate

C = Total Integrated Peak Count

R = Ratio of Scan Time to background counting time

B = Total Background Count

Lp = Lorentz-polarization factor

p = p-factor

(4) Standard deviation of an observation of unit weight:

$$\sqrt{\Sigma w(|Fo| - |Fc|)^2 / (No - Nv)}$$

where: No = number of observations

Nv = number of variables

(5) Cromer, D. T. & Waber, J. T.; "International Tables for X-ray Crystallography", Vol. IV, The Kynoch Press, Birmingham, England, Table 2.2 A (1974).

(6) Ibers, J. A. & Hamilton, W. C.; Acta Crystallogr., 17, 781 (1964).

(7) Creagh, D. C. & McAuley, W.J.; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.6.8, pages 219-222 (1992).

(8) Creagh, D. C. & Hubbell, J.H.; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.4.3, pages 200-206 (1992).

(9) teXsan: Crystal Structure Analysis Package, Molecular Structure Corporation (1985 & 1992).

A. Crystal Data

Empirical Formula	C ₁₁ H ₁₃ O ₂ Br ₂ F
Formula Weight	356.03
Crystal Color, Habit	colorless, prismatic
Crystal Dimensions	0.40 X 0.20 X 0.15 mm
Crystal System	orthorhombic
Lattice Type	Primitive
No. of Reflections Used for Unit Cell Determination (2θ range)	25 (20.3 - 24.7°)
Omega Scan Peak Width at Half-height	0.12°
Lattice Parameters	a = 10.205(2) Å b = 13.237(3) Å c = 9.538(2) Å V = 1288.4(3) Å ³
Space Group	P2 ₁ 2 ₁ 2 ₁ (#19)
Z value	4
D _{calc}	1.835 g/cm ³
F ₀₀₀	696.00
μ(MoKα)	63.06 cm ⁻¹

B. Intensity Measurements

Diffractometer	Rigaku AFC5S
Radiation	MoKα (λ = 0.71069 Å) graphite monochromated
Attenuator	Zr foil (factors = 1.00, 3.38, 11.56, 39.32)

Take-off Angle	6.0°
Detector Aperture	9.0 mm horizontal 13.0 mm vertical
Crystal to Detector Distance	258 mm
Temperature	23.0°C
Scan Type	ω-2θ
Scan Rate	8.0°/min (in ω) – up to 5 scans
Scan Width	(1.10 + 0.50 tan θ)°
2θ _{max}	55.0°
No. of Reflections Measured	Total: 1724
Corrections	Lorentz-polarization Absorption (trans. factors: 0.5279 - 0.9996)

C. Structure Solution and Refinement

Structure Solution	Patterson Methods (DIRDIF92 PATTY)
Refinement	Full-matrix least-squares
Function Minimized	Σw(F _o – F _c) ²
Least Squares Weights	$\frac{1}{\sigma^2(F_o)} = \frac{4F_o^2}{\sigma^2(F_o^2)}$
p-factor	0.00
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>3.00σ(I))	850
No. Variables	145
Reflection/Parameter Ratio	5.86
Residuals: R; Rw	0.038 ; 0.025
Goodness of Fit Indicator	1.85
Max Shift/Error in Final Cycle	0.00
Maximum peak in Final Diff. Map	0.53 e ⁻ /Å ³

Minimum peak in Final Diff. Map -0.39 $e^-/\text{\AA}^3$

Table 1. Atomic coordinates and B_{iso}/B_{eq}

atom	x	y	z	B_{eq}
Br(1)	0.0042(1)	0.47534(10)	-0.0663(1)	5.61(3)
Br(2)	0.1113(1)	0.3687(1)	-0.3369(1)	5.15(3)
F(1)	0.2446(5)	0.3974(4)	-0.0969(6)	4.0(2)
O(1)	-0.0517(6)	0.2476(6)	-0.0764(8)	4.0(2)
O(2)	0.2857(6)	0.1982(5)	-0.1586(7)	3.0(2)
C(1)	0.123(1)	0.3677(8)	-0.1360(9)	3.1(3)
C(2)	0.0850(10)	0.2673(9)	-0.072(1)	3.1(3)
C(3)	0.151(1)	0.1773(8)	-0.136(1)	3.8(3)
C(4)	0.133(1)	0.0814(8)	-0.047(1)	5.4(3)
C(5)	0.339(1)	0.1492(9)	-0.278(1)	4.2(3)
C(6)	0.477(1)	0.1845(9)	-0.304(1)	3.3(3)
C(7)	0.581(1)	0.1199(9)	-0.294(1)	4.3(3)
C(8)	0.709(1)	0.157(1)	-0.309(1)	5.5(4)
C(9)	0.728(1)	0.257(1)	-0.330(1)	5.1(4)
C(10)	0.623(1)	0.3215(8)	-0.342(1)	4.9(3)
C(11)	0.497(1)	0.2865(9)	-0.326(1)	4.4(3)
H(1)	0.1098	0.2692	0.0242	3.9060
H(2)	0.1115	0.1655	-0.2250	3.7630
H(3)	0.0420	0.0680	-0.0355	3.5515
H(4)	0.1722	0.0911	0.0422	3.5515
H(5)	0.1733	0.0258	-0.0928	3.5515
H(6)	0.3391	0.0783	-0.2630	4.2089
H(7)	0.2865	0.1644	-0.3578	4.2089
H(8)	0.5668	0.0501	-0.2766	5.5248

Table 1. Atomic coordinates and B_{iso}/B_{eq} (continued)

atom	x	y	z	B_{eq}
H(9)	0.7821	0.1120	-0.3055	5.0924
H(10)	0.8149	0.2828	-0.3360	6.6116
H(11)	0.6371	0.3909	-0.3623	5.3468
H(12)	0.4246	0.3318	-0.3291	4.8470
H(13)	-0.0972	0.2895	-0.0041	-0.4443

$$B_{eq} = \frac{8}{3}\pi^2(U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}aa^*bb^*\cos\gamma + 2U_{13}aa^*cc^*\cos\beta + 2U_{23}bb^*cc^*\cos\alpha)$$

Table 2. Anisotropic Displacement Parameters

atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Br(1)	0.0810(9)	0.0563(8)	0.0759(9)	0.0218(10)	0.0297(10)	0.0072(9)
Br(2)	0.0725(9)	0.080(1)	0.0436(6)	0.0197(10)	0.0079(8)	0.0140(9)
F(1)	0.038(4)	0.044(4)	0.071(4)	-0.008(3)	-0.001(3)	0.002(4)
O(1)	0.031(4)	0.060(6)	0.059(5)	0.001(4)	0.008(4)	-0.003(5)
O(2)	0.029(4)	0.050(5)	0.035(4)	-0.001(4)	0.003(4)	-0.009(4)
C(1)	0.053(7)	0.035(7)	0.031(6)	0.019(7)	0.003(6)	0.003(6)
C(2)	0.036(7)	0.051(8)	0.030(6)	-0.014(7)	0.005(6)	-0.018(7)
C(3)	0.060(9)	0.036(8)	0.049(8)	0.005(7)	0.006(7)	-0.002(7)
C(4)	0.077(9)	0.039(8)	0.091(9)	-0.004(8)	0.000(9)	0.004(8)
C(5)	0.056(9)	0.051(9)	0.051(8)	-0.002(8)	0.000(6)	0.001(8)
C(6)	0.029(7)	0.049(8)	0.049(7)	0.004(7)	0.004(6)	-0.002(7)
C(7)	0.08(1)	0.041(9)	0.044(7)	0.020(8)	0.009(7)	0.000(7)
C(8)	0.07(1)	0.07(1)	0.067(10)	0.029(10)	0.021(8)	0.005(10)
C(9)	0.054(9)	0.10(1)	0.041(7)	-0.002(10)	-0.009(8)	0.00(1)
C(10)	0.069(9)	0.051(9)	0.065(8)	-0.005(9)	-0.004(9)	0.017(8)
C(11)	0.040(7)	0.058(9)	0.069(8)	0.001(8)	0.002(9)	0.003(8)

The general temperature factor expression:

$$\exp(-2\pi^2(a^{*2}U_{11}h^2 + b^{*2}U_{22}k^2 + c^{*2}U_{33}l^2 + 2a^*b^*U_{12}hk + 2a^*c^*U_{13}hl + 2b^*c^*U_{23}kl))$$

Table 3. Bond Lengths(\AA)

atom	atom	distance	atom	atom	distance
Br(1)	C(1)	1.987(10)	Br(2)	C(1)	1.920(8)
F(1)	C(1)	1.35(1)	O(1)	C(2)	1.42(1)
O(2)	C(3)	1.42(1)	O(2)	C(5)	1.42(1)
C(1)	C(2)	1.52(1)	C(2)	C(3)	1.50(1)
C(3)	C(4)	1.54(1)	C(5)	C(6)	1.50(1)
C(6)	C(7)	1.37(1)	C(6)	C(11)	1.38(1)
C(7)	C(8)	1.41(2)	C(8)	C(9)	1.35(2)
C(9)	C(10)	1.38(2)	C(10)	C(11)	1.37(2)

Table 4. Bond Lengths(\AA)

atom	atom	distance	atom	atom	distance
O(1)	H(15)	1.00	C(2)	H(1)	0.95
C(3)	H(2)	0.95	C(4)	H(3)	0.95
C(4)	H(4)	0.95	C(4)	H(5)	0.95
C(5)	H(6)	0.95	C(5)	H(7)	0.95
C(7)	H(8)	0.95	C(8)	H(9)	0.95
C(9)	H(10)	0.95	C(10)	H(11)	0.95
C(11)	H(12)	0.95			

Table 5. Bond Angles(°)

atom	atom	atom	angle	atom	atom	atom	angle
C(3)	O(2)	C(5)	113.7(8)	Br(1)	C(1)	Br(2)	106.9(5)
Br(1)	C(1)	F(1)	105.1(7)	Br(1)	C(1)	C(2)	109.6(7)
Br(2)	C(1)	F(1)	109.4(7)	Br(2)	C(1)	C(2)	113.1(8)
F(1)	C(1)	C(2)	112.4(9)	O(1)	C(2)	C(1)	113(1)
O(1)	C(2)	C(3)	106.3(9)	C(1)	C(2)	C(3)	114.6(8)
O(2)	C(3)	C(2)	109.9(9)	O(2)	C(3)	C(4)	111.1(10)
C(2)	C(3)	C(4)	112.1(9)	O(2)	C(5)	C(6)	110.3(9)
C(5)	C(6)	C(7)	121(1)	C(5)	C(6)	C(11)	117(1)
C(7)	C(6)	C(11)	120(1)	C(6)	C(7)	C(8)	120(1)
C(7)	C(8)	C(9)	119(1)	C(8)	C(9)	C(10)	120(1)
C(9)	C(10)	C(11)	120(1)	C(6)	C(11)	C(10)	119(1)

Table 6. Bond Angles(°)

atom	atom	atom	angle	atom	atom	atom	angle
C(2)	O(1)	H(15)	109.5	O(1)	C(2)	H(1)	107.3
C(1)	C(2)	H(1)	107.3	C(3)	C(2)	H(1)	107.3
O(2)	C(3)	H(2)	107.9	C(2)	C(3)	H(2)	107.9
C(4)	C(3)	H(2)	107.9	C(3)	C(4)	H(3)	109.5
C(3)	C(4)	H(4)	109.5	C(3)	C(4)	H(5)	109.5
H(3)	C(4)	H(4)	109.5	H(3)	C(4)	H(5)	109.5
H(4)	C(4)	H(5)	109.5	O(2)	C(5)	H(6)	109.3
O(2)	C(5)	H(7)	109.3	C(6)	C(5)	H(6)	109.3
C(6)	C(5)	H(7)	109.3	H(6)	C(5)	H(7)	109.5
C(6)	C(7)	H(8)	120.0	C(8)	C(7)	H(8)	120.0
C(7)	C(8)	H(9)	120.4	C(9)	C(8)	H(9)	120.4
C(8)	C(9)	H(10)	119.7	C(10)	C(9)	H(10)	119.7
C(9)	C(10)	H(11)	119.7	C(11)	C(10)	H(11)	119.7
C(6)	C(11)	H(12)	120.5	C(10)	C(11)	H(12)	120.5

Table 7. Torsion Angles(°)

atom	atom	atom	atom	angle	atom	atom	atom	atom	angle
Br(1)	C(1)	C(2)	O(1)	46(1)	Br(1)	C(1)	C(2)	C(3)	169.1(7)
Br(2)	C(1)	C(2)	O(1)	-72.7(10)	Br(2)	C(1)	C(2)	C(3)	49(1)
F(1)	C(1)	C(2)	O(1)	162.9(8)	F(1)	C(1)	C(2)	C(3)	-74(1)
O(1)	C(2)	C(3)	O(2)	169.6(9)	O(1)	C(2)	C(3)	C(4)	-66(1)
O(2)	C(3)	C(2)	C(1)	43(1)	O(2)	C(5)	C(6)	C(7)	115(1)
O(2)	C(5)	C(6)	C(11)	-58(1)	C(1)	C(2)	C(3)	C(4)	167.1(10)
C(2)	C(3)	O(2)	C(5)	-147.6(8)	C(3)	O(2)	C(5)	C(6)	173.5(9)
C(4)	C(3)	O(2)	C(5)	87(1)	C(5)	C(6)	C(7)	C(8)	-175(1)
C(5)	C(6)	C(11)	C(10)	176(1)	C(6)	C(7)	C(8)	C(9)	1(2)
C(6)	C(11)	C(10)	C(9)	-3(1)	C(7)	C(6)	C(11)	C(10)	2(1)
C(7)	C(8)	C(9)	C(10)	-3(2)	C(8)	C(7)	C(6)	C(11)	-1(1)
C(8)	C(9)	C(10)	C(11)	3(2)					

2-7 References

- Reviews on the carbenoid chemistry: a) W. Kirmse, *Angew. Chem. Int. Ed. Engl.*, **4**, 1 (1965); b) G. Köbrich, *Angew. Chem. Int. Ed. Engl.*, **6**, 41 (1967); c) G. Köbrich, *Bull. Soc. Chim. Fr.*, 2712 (1969); d) T. Chivers, *Organometal. Chem. Rev. A*, **6**, 1 (1970); e) J. Villieras, *Organometal. Chem. Rev. A*, **7**, 81 (1971); f) G. Köbrich, *Angew. Chem. Int. Ed. Engl.*, **11**, 473 (1972); g) A. Krief, *Tetrahedron*, **36**, 2531 (1980); h) H. Siegel, in "Topics in Current Chemistry," ed. by Springer-Verlag, Berlin (1982), Vol. 106, p 55; i) K. G. Taylor, *Tetrahedron*, **38**, 2751 (1982); j) H. Nozaki, *Synlett*, 441 (1990); k) W. B. Motherwell and C. J. Nutley, *Contemporary Organic Synthesis*, **1**, 219 (1994).
- Reviews on fluorinated organometallics: a) D. J. Burton and Z.-Y. Yang, *Tetrahedron*, **48**, 189 (1992); b) D. J. Burton, Z.-Y. Yang, and P. A. Morken, *Tetrahedron*, **50**, 2993 (1994).
- Reviews on the organofluorine chemistry: a) "Fluorine-Containing Molecules. Structure, Reactivity, Synthesis, and Applications.," ed. by J. F. Liebman, A. Greenberg, and W. R. Dolbier, VCH, New York (1988); b) "Selective Fluorination in Organic and Bioorganic Chemistry," ed. by J. T. Welch, American Chemical Society, Washington, DC (1991); c) M. Hudlicky, "Chemistry of Organic Fluorine Compounds. 2nd (Revised) Edition," Ellis Horwood, New York (1992); d) "Organofluorine Chemistry. Principles and Commercial Applications," ed. by R. E. Banks, B. E. Smart, and J. C. Tatlow, Plenum Press, New York (1994); e) "Chemistry of Organic Fluorine Compounds II. A Critical Review," ed. by M. Hudlicky and A. E. Pavlath, American Chemical Society, Washington, DC (1995). For reviews on the synthesis of organofluorine compounds: f) J. T. Welch, *Tetrahedron*, **43**, 3123 (1987); g) P. Bravo and G. Resnati, *Tetrahedron: Asymmetry*, **1**, 661 (1990); h) J. A. Wilkinson, *Chem. Rev.*, **92**, 505 (1992); i) G. Resnati, *Tetrahedron*, **49**, 9385 (1993); j) J. M. Percy, *Contemporary Organic Synthesis*, **2**, 251 (1995); k) M. J. Tozer and T. F. Herpin, *Tetrahedron*, **52**, 8619 (1996).
- For the computational study on structures and stabilities of α -heteroatom-substituted organolithium compounds, see: P. V. R. Schleyer, T. Clark, A. J. Kos, G. W. Spitznagel, C. Rohde, D. Arad, K. N. Houk, and N. G. Rondan, *J. Am. Chem. Soc.*, **106**, 6467 (1984).
- For review on fluorinated carbenes, see: a) D. L. S. Brahms and W. P. Dailey, *Chem. Rev.*, **96**, 1585 (1996). Examples of fluorohalocarbenes generated from the carbenoid reagent of Li: b) M. Schlosser and G. Heinz, *Angew. Chem. Int. Ed.*

- Engl.*, **6**, 629 (1967); c) M. Schlosser and G. Heinz, *Angew. Chem. Int. Ed. Engl.*, **7**, 820 (1968); d) M. Schlosser and G. Heinz, *Chem. Ber.*, **104**, 1934 (1971); e) D. J. Burton and J. L. Hahnfeld, *J. Org. Chem.*, **42**, 828 (1977). Those of Zn: f) J. Nishimura and J. Furukawa, *J. Chem. Soc., Chem. Commun.*, **1971**, 1375; g) S. Elsheimer and J. W. R. Dolbier, *J. Fluorine Chem.*, **40**, 119 (1988); h) O. Tamura, M. Hashimoto, Y. Kobayashi, T. Katoh, K. Nakatani, M. Kumada, I. Hayakawa, T. Akiba, and S. Terashima, *Tetrahedron Lett.*, **33**, 3483 (1992); i) O. Tamura, M. Hashimoto, Y. Kobayashi, T. Katoh, K. Nakatani, M. Kumada, I. Hayakawa, T. Akiba, and S. Terashima, *Tetrahedron*, **50**, 3889 (1994); j) T. Akiba, O. Tamura, M. Hashimoto, Y. Kobayashi, T. Katoh, K. Nakatani, M. Kumada, I. Hayakawa, and S. Terashima, *Tetrahedron*, **50**, 3905 (1994). Examples of Ti: k) J. W. R. Dolbier and C. R. Burkholder, *Tetrahedron Lett.*, **29**, 6749 (1988); l) J. W. R. Dolbier and C. R. Burkholder, *J. Org. Chem.*, **55**, 589 (1990). Those of Hg: m) D. Seyferth, C. K. Haas, and S. P. Hopper, *J. Organomet. Chem.*, **33**, C1 (1971); n) D. Seyferth and S. P. Hopper, *J. Organomet. Chem.*, **51**, 77 (1973).
- 6) Fluorinated carbenoids with (RO)₂PO-, PhSO-, or PhSO₂- undergo nucleophilic reaction toward with carbonyl compounds and alkyl halides. D. J. Burton, Z.-Y. Yang, and W. Qiu, *Chem. Rev.*, **96**, 1641 (1996).
- 7) Monofluoro building blocks are reviewed in: a) Takeuchi, Y. *Yuki Gosei Kagaku Kyokai Shi.*, **46**, 145 (1988). For the synthesis of fluorinated compounds using tribromofluoromethane: a) R. W. Vanderhaar, D. J. Burton, and D. G. Nae, *J. Fluorine Chem.*, **1**, 381 (1972); b) J. P. Sloan, J. M. Tedder, and J. C. Walton, *J. Chem. Soc., Faraday Trans. 1*, **69**, 1143 (1973); c) D. J. Burton and R. M. Flynn, *J. Fluorine Chem.*, **10**, 329 (1977); d) D. J. Burton and J. L. Hahnfeld, *J. Org. Chem.*, **42**, 828 (1977); e) Y. Katsuhara and D. D. DesMarteau, *J. Am. Chem. Soc.*, **102**, 2681 (1980); f) D. J. Burton, S. Shin-Ya, and H. S. Kesling, *J. Fluorine Chem.*, **20**, 89 (1982); g) D. J. Burton, *J. Fluorine Chem.*, **23**, 339 (1983); h) D. J. Burton and D. M. Wiemers, *J. Fluorine Chem.*, **27**, 85 (1985); i) I. H. Jeong, D. J. Burton, and D. G. Cox, *Tetrahedron Lett.*, **27**, 3709 (1986); j) D. G. Cox and D. J. Burton, *J. Org. Chem.*, **53**, 366 (1988); k) D. Su, W. Cen, R. L. Kirchmeier, and J. M. Shreeve, *Can. J. Chem.*, **67**, 1795 (1989); l) H. Bürger and P. Moritz, *Organometallics*, **12**, 4930 (1993); m) C. Patois and P. Savignac, *J. Chem. Soc., Chem. Commun.*, **1993**, 1711; n) C. Patois and P. Savignac, *Synth. Commun.*, **24**, 1317 (1994); o) J. Nieschalk and D. O'Hagan, *J. Chem. Soc., Chem. Commun.*, **1995**, 719; p) J. Nieschalk, A. S. Batsanov, D. O'Hagan, and

- J. A. K. Howard, *Tetrahedron*, **52**, 165 (1996); q) R. Waschbusch, J. Carran, and P. Savignac, *Tetrahedron*, **52**, 14199 (1996).
- 8) a) G. Cainelli, A. U. Ronchi, F. Bertini, P. Grasselli, and G. Zubiani, *Tetrahedron*, **27**, 6109 (1971); b) J. Villieras, C. Bacquet, D. Masure, and J. F. Normant, *J. Organomet. Chem.*, **50**, C7 (1973); c) J. Villieras, C. Bacquet, and J. F. Normant, *Bull. Soc. Chim. Fr.*, **1975**, 1797; d) R. Tarhouni, B. Kirschleger, M. Rambaud, and J. Villieras, *Tetrahedron Lett.*, **25**, 835 (1984); e) T. J. Michnick and D. S. Matteson, *Synlett*, **1991**, 631; f) P. L. Beaulieu and D. Wernic, *J. Org. Chem.*, **61**, 3635 (1996).
- 9) B. E. Smart, in "Organofluorine Chemistry—Principles and Commercial Applications," ed by R. E. Banks, B. E. Smart, and J. C. Tatlow, Plenum Press, New York (1994), Vol. p 57.
- 10) "Fluorine in Organic Chemistry" ed by R. D. Chambers, John Wiley & Sons. Inc., New York (1973).
- 11) Recent review of zinc carbenoids: W. B. Motherwell, and C. J. Nutley, *Contemporary Organic Synthesis*, **1**, 219 (1994).
- 12) Pioneering works with diethylzinc as the reducing reagent are: a) J. Furukawa, N. Kawabata, and J. Nishimura, *Tetrahedron Lett.*, **28**, 3353 (1966); b) J. Furukawa, N. Kawabata, and J. Nishimura, *Tetrahedron*, **24**, 53 (1968). Structural studies on (halomethyl)zinc reagents are: c) S. E. Denmark, J. P. Edwards, and S. R. Wilson, *J. Am. Chem. Soc.*, **113**, 723 (1991); d) S. E. Denmark, J. P. Edwards, and S. R. Wilson, *J. Am. Chem. Soc.*, **114**, 2592 (1992); e) A. B. Charette, and J. Marcoux, *J. Am. Chem. Soc.*, **118**, 4539 (1996); f) A. B. Charette, J. Marcoux, and F. Belanger-Gariepy, *J. Am. Chem. Soc.*, **118**, 6792 (1996). Use of zinc carbenoids for the synthesis of fluorocyclopropanes, see: e) O. Tamura, M. Hashimoto, Y. Kobayashi, T. Katoh, K. Nakatani, M. Kumada, I. Hayakawa, T. Akiba, and S. Terashima, *Tetrahedron Lett.*, **33**, 3483 (1992); f) O. Tamura, M. Hashimoto, Y. Kobayashi, T. Katoh, K. Nakatani, M. Kumada, I. Hayakawa, T. Akiba, and S. Terashima, *Tetrahedron*, **50**, 3889 (1994); g) T. Akiba, O. Tamura, M. Hashimoto, Y. Kobayashi, T. Katoh, K. Nakatani, M. Kumada, I. Hayakawa, and S. Terashima, *Tetrahedron*, **50**, 3905 (1994).
- 13) The fact that zinc carbenoid **2** is more stable than the corresponding lithium carbenoid may be attributed to the interaction between zinc and halogen was decreased by the coordination of DMF to zinc. As a supplement, 1,1,1-trichloro-2,2,2-trifluoroethane with zinc metal in DMF generated a thermally stable zinc carbenoid reagent CF₃CCl₂ZnCl, which was coordinated with oxygen atom of two

DMF molecule by X-ray analysis.²⁰⁾

- 14) M. Fujita, M. Obayashi, and T. Hiyama, *Tetrahedron*, **44**, 4135 (1988).
- 15) J. Uenishi and M. Yamamoto, *Yuki Gosei Kagaku Kyokai Shi*, **43**, 355 (1985).
- 16) M. T. Reetz, *Angew. Chem. Int. Ed. Engl.*, **23**, 556 (1984).
- 17) a) M. Cherest, H. Felkin, and N. Prudent, *Tetrahedron Lett.*, **30**, 2199 (1968); b) N. T. Anh, *Top. Curr. Chem.* **88**, 145 (1980).
- 18) The presence of LiBr is reported to stabilize a lithium carbenoid. R. Tarhouni, B. Kirschleger, M. Rambaud, and Villieras, *J. Tetrahedron Lett.*, **25**, 835 (1984).
- 19) Discrimination of aldehydes from ketones by organometallic reagents of B: a) H. C. Brown, U. R. Khire, G. Narla, and U. S. Racherla, *J. Org. Chem.*, **60**, 544 (1995). Mg: b) M. T. Reetz, N. Harmat, and R. Mahrwald, *Angew. Chem. Int. Ed. Engl.*, **31**, 342 (1992). Cr: c) Y. Okude, S. Hirano, T. Hiyama, and H. Nozaki, *J. Am. Chem. Soc.*, **99**, 3179 (1977); d) T. Hiyama, Y. Okude, K. Kimura, and H. Nozaki, *Bull. Chem. Soc. Jpn.*, **55**, 561 (1982); e) K. Takai, K. Kimura, T. Kuroda, T. Hiyama, and H. Nozaki, *Tetrahedron Lett.*, **24**, 5281 (1983); f) K. Takai, T. Kuroda, S. Nakatsukasa, K. Oshima, and H. Nozaki, *Tetrahedron Lett.*, **26**, 5585 (1985). Ti: g) M. T. Reetz, *Organotitanium Reagents in Organic Synthesis*; Springer-Verlag: Berlin, chapter 3 (1986); h) T. Kauffmann, T. Abel, W. Li, G. Neiteler, M. Schreer, and D. Schwarze, *Chem. Ber.*, **126**, 459 (1993). Cu: i) Y. Yamamoto, S. Yamamoto, H. Yatagai, Y. Ishihara, and K. Maruyama, *J. Org. Chem.*, **47**, 119 (1982). Zn: j) Y. Gao, H. Urabe, and F. Sato, *J. Org. Chem.*, **59**, 5521 (1994). Sn: k) A. Yanagisawa, H. Inoue, M. Morodome, and H. Yamamoto, *J. Am. Chem. Soc.*, **115**, 10356 (1993). Pb: l) Y. Yamamoto and J.-i. Yamada, *J. Am. Chem. Soc.*, **109**, 4395 (1987). Bi: m) M. Wada, H. Ohki, and K.-y. Akiba, *Tetrahedron Lett.*, **27**, 4771 (1986). Zn/Ti and Zn/Al: n) T. Okazoe, J.-i. Hibino, K. Takai, and H. Nozaki, *Tetrahedron Lett.*, **26**, 5581 (1985).
- 20) D. Bellus, B. Klingert, R. W. Lang, and G. Rihs, *J. Organomet. Chem.* **339**, 17 (1988).

Chapter 3

Diastereoselective Generation of Carbenoid Reagent RCH(OMEM)CFBrLi and Reaction with Electrophiles

Treatment of RCH[OCH₂O(CH₂)₂OCH₃]CFBr₂ derived from fluorinated alcohols RHC(OH)CFBr₂ with butyllithium at -130 °C in the presence of 4-heptanone gave selectively *syn*-isomers of RCH[OCH₂O(CH₂)₂OCH₃]CFBrC(OH)Pr₂. The stereochemical outcome is explained in terms of selective lithium-bromine exchange via a chelation between lithium and oxygen atoms of the (2-methoxyethoxy)methyl group. Starting with 2-phenylpropanal, a product is obtained highly selectively that contains three contiguous stereocenters including a -CFBr- moiety.

3-1 Introduction

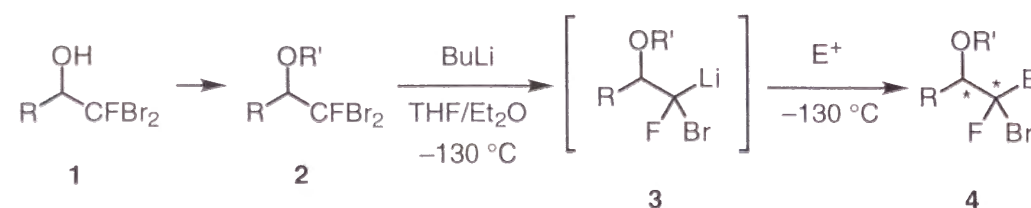
In view of the unique influence of fluorine on biological activity,¹⁾ synthesis of chiral fluoroorganic compounds contributes greatly to biological and medicinal chemistry. Due to high electronegativity, fluorine has a remarkable electronic effect towards its neighbor within a molecule. For example, introduction of fluorine at an sp^3 or sp^2 carbon of bioactive compounds frequently leads to discovery of novel and/or potent biochemical tools and medicinal agents.²⁾ The resulting fluoro compounds often become chiral. However, it is generally difficult to control the stereochemistry of a -CFH- moiety. Although Welch reported the synthesis of α -fluoro- β -hydroxy ketones by aldol reaction of lithium enolates derived from fluoro ketones,³⁾ the diastereoselectivity is not high enough. He also studied the synthesis of 2-deoxy-2-fluoro-*ribo*-D-pentopyranose through the aldol type reaction of ethyl fluoroacetate with glyceraldehyde acetonide followed by deprotection of the glycol and reduction of the ester,⁴⁾ but the selectivity remains yet to be improved. Thus, the development of a stereoselective synthesis of -CFH- moiety is important. In addition, stereoselective synthesis of a -CFBr- moiety also is a recent topic.⁵⁾

The Author envisaged selective lithium-bromine exchange in **1** and subsequent stereospecific reaction with an electrophile, if possible, would provide us with a novel method for stereoselective construction of a -CFBr- moiety.

3-2 Diastereoselective Generation of RCH(OMEM)CFBrLi and Reaction with Electrophiles

To realize the idea, the Author first protected the hydroxy group of **1** and obtained the corresponding silyl, methyl, methoxymethyl (MOM), and (2-methoxyethoxy)methyl (MEM) ethers **2**. As the bromine-lithium exchange of 1,1-dibromoalkanes containing a 3-alkoxy⁶⁾ or 2-silyloxy group⁷⁾ is known to occur diastereoselectively, the Author studied the diastereoselective generation of lithium carbenoid **3** from **2** and its reaction with electrophiles as shown in Scheme 3-1.

Scheme 3-1. Diastereoselective generation of **3** and reactions with electrophiles.



A solution of **2** and 4-heptanone in THF-Et₂O (2 : 1) was treated with butyllithium at -130 °C. The resulting mixture was stirred for 1 h at -130 °C and allowed to warm up to -78 °C before quenching with sat. NH₄Cl aq. solution. Workup and purification gave the corresponding alcohol **4** as a diastereomeric mixture. The results are summarized in Table 3-1.

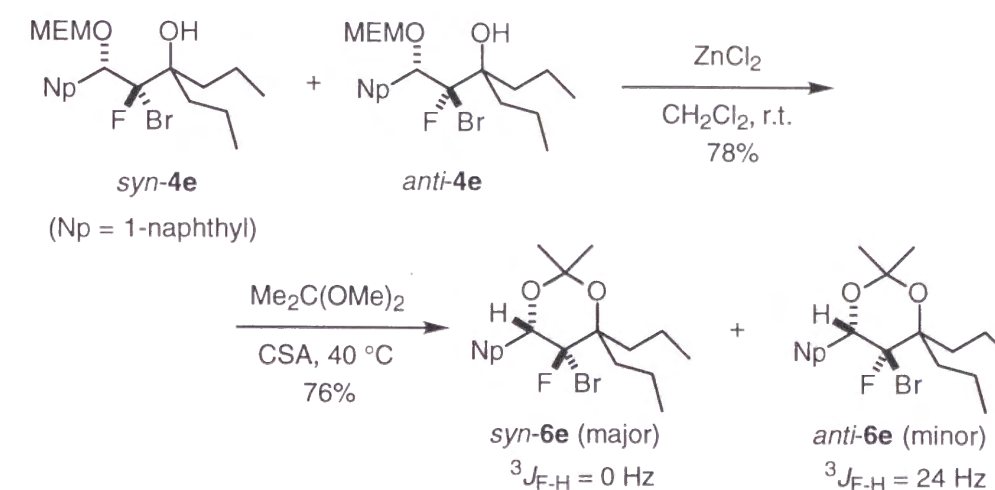
Silyl and methyl ethers **2a~2e** reacted with 4-heptanone to give **4a~4e** with 57~67% *syn*-selectivities. It is particularly worthy of noting that silyl ethers **2a** and **2b** afforded oxiranes **5a** and **5b**, respectively. It is proposed that these were produced from *anti*-**4a** and **4b**, respectively, via intramolecular cyclization. On the other hand, MOM ether **2d** and MEM ether **2e**, having one or two ethereal oxygen(s) afforded *syn*-**4d** and **4e**, respectively, with relatively high diastereoselectivity. These results show that the protecting groups play an important role in the diastereoselective generation of lithium carbenoid **3**.^{8,9)} The diastereoselectivity is also affected by substituent R. Substrate **2f** or **2g** exhibited moderate selectivity, whereas high *syn*-selectivity was observed with **2h** or **2i**. Thus, with bulkier substituent R, higher *syn*-diastereoselectivity resulted. The yields were generally moderate, probably because fluorine-containing carbenoid **3** was thermally labile even at -130 °C and possibly underwent proton abstraction from 4-heptanone.

The stereochemistry of **4e** was assigned on the basis of ¹H and ¹⁹F NMR spectroscopy of acetonide **6** prepared through deprotection followed by acetalization as shown in Scheme 3-2. Thus, one vicinal coupling constant ³J_{F-H} of the major isomer of **6** was smaller than that of the minor isomer, and this observation shows that fluorine and hydrogen atoms of the minor isomer are positioned *anti*. Accordingly, the stereochemistry of the major diastereomer of **4e** was assigned *syn*.¹⁰⁾

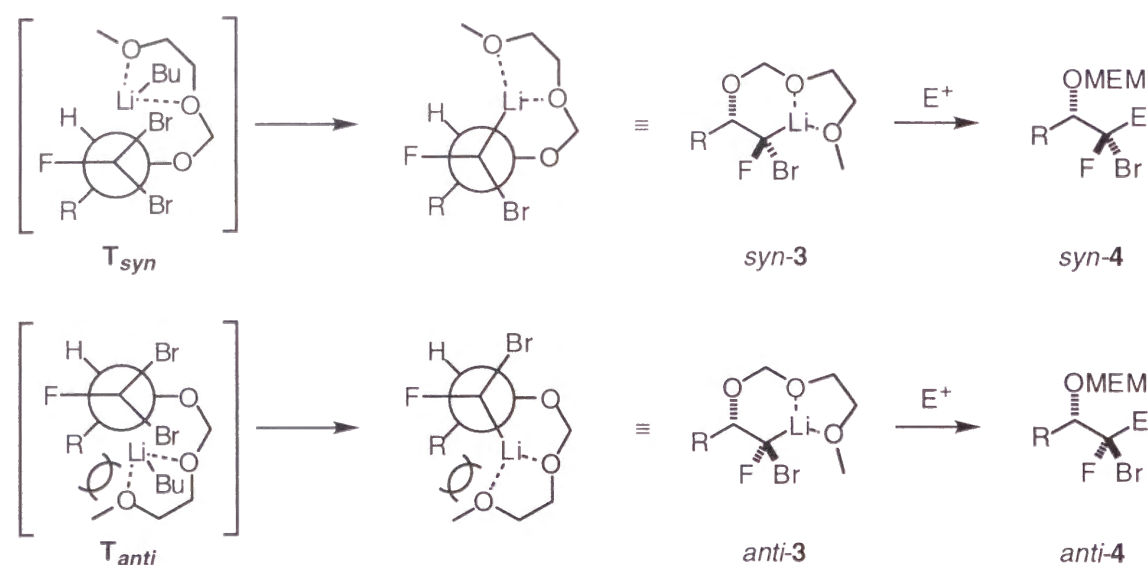
Table 3-1. Diastereoselectivity in the bromine-lithium exchange of $\text{RCH}(\text{OR}')\text{CFBr}_2$ (2) followed by the reaction with 4-heptanone.^{a)}

run	substrate		yield/% ^{b)}	product ratio ^{c)}	
	R	R'		syn-4	anti-4
1	2a	1-naphthyl-	38	57	25
2	2b	1-naphthyl-	47	67	0
3	2c	1-naphthyl-	49	60	40
4	2d	1-naphthyl-	55	85	15
5	2e	1-naphthyl-	55	83	17
6	2f	Ph-	58	50	50
7	2g	$\text{Ph}(\text{CH}_2)_2$ -	62	62	38
8	2h	c-Hex-	51	92	8
9	2i	i-Pr-	46	92	8

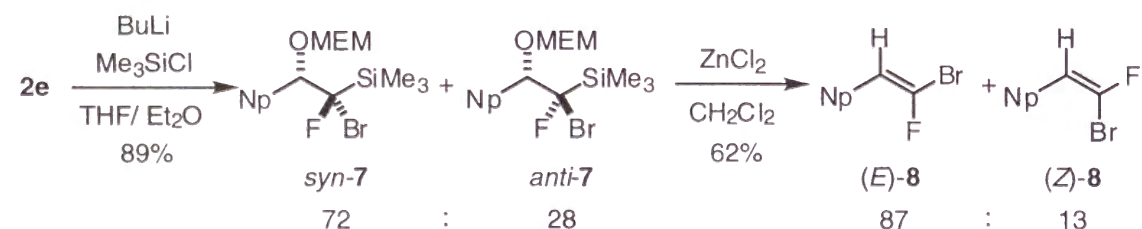
a) Butyllithium was added to a solution of 2 and 4-heptanone in THF-Et₂O (2 : 1) at -130 °C. b) Isolated yield. c) The diastereomeric ratio was determined by ¹⁹F NMR.

Scheme 3-2. Stereochemical Assignment of 4e.

The stereochemical outcome is tentatively attributed to the chelation effect as illustrated in Scheme 3-3.¹¹⁾ The Author assumes that the conformations in which the carbon-fluorine bond and carbon-oxygen bond are oriented *anti* are favorable due to the dipole-dipole repulsion between these bonds.¹²⁾ Thus, two transition states, **T_{syn}** and **T_{anti}**, are possible.¹³⁾ While **T_{anti}** involves the steric interaction between substituent R and the lithium chelating with the MEM group, such interaction is absent in **T_{syn}**. Accordingly, exchange of *pro*-(R)-bromine-lithium with retention of configuration proceeds preferentially *via* **T_{syn}**, and the resulting carbenoid, *syn-3*, undergoes carbonyl addition with retention of configuration to give rise to *syn-4*. Based on the transition state model of **T_{syn}**, it can reasonably be explained that the sense of diastereoselectivity should be *syn* and the degree of the selectivity should depend on the size of substituent R.

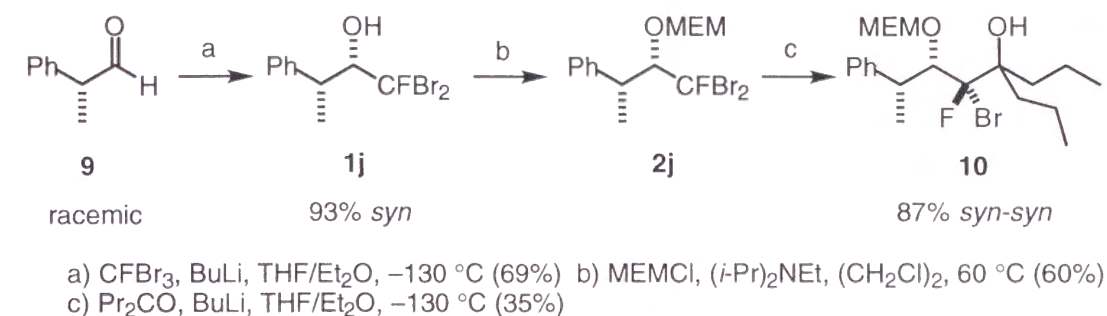
Scheme 3–3. Transition states in the diastereoselective bromine-lithium exchange of **2**.

Silylation of **2e** with chlorotrimethylsilane also occurred stereoselectively to give *syn*-**7** as the major diastereomer in a good yield (Scheme 3–4). The stereochemistry of **7** was determined by the conversion of **7** into **8** with zinc chloride through deprotection of the MEM group and the Peterson elimination in one-pot, followed by ^1H NMR analysis of $^3J_{\text{H-F}}$ of **8**.

Scheme 3–4. Silylation of **2e** and olefination.

Finally, the Author explored the stereocontrol of three contiguous chiral centers starting with (\pm)-2-phenylpropanal (**9**) as the substrate (Scheme 3–5). Treatment of tribromofluoromethane with butyllithium at $-130\text{ }^\circ\text{C}$ in the presence of **9** gave with 93% *syn*-selectivity **1j**,¹⁴⁾ whose hydroxy group was protected by an MEM group. The resulting MEM ether, **2j**, was treated with butyllithium and 4-heptanone to give **10** with 87% selectivity. The stereochemistry of **10** was deduced to be *syn-syn* in analogy

with the results of the reaction of **2**.

Scheme 3–5. Diastereocontrol of three contiguous stereocenters.

3–3 Summary

Protection of **1** with an MEM group followed by lithiation of resulting MEM ethers **2** and the subsequent reaction with various electrophiles are found to proceed diastereoselectively. The present method involving a fluorine-substituted lithium carbenoid and its reaction with electrophiles constitutes a highly efficient route to stereo-defined construction of organofluorine compounds containing a -CFBr- moiety.

3-4 Experimental

1,1-Dibromo-1-fluoro-2-(1-naphthyl)-2-(triethylsiloxy)ethane (2a)

A 50 ml two-necked round-bottomed flask was charged with 2,2-dibromo-2-fluoro-1-(naphthyl)ethanol (0.31 g, 0.89 mmol), imidazole (0.136 g, 2.0 mmol), 4-dimethylaminopyridine (ca. 10 mg), and DMF (5 ml) under an argon atmosphere. Chlorotriethylsilane (0.34 ml, 2.0 mmol) was added to the solution. The reaction mixture was heated for 1 h at 60 °C and then poured into water. The organic layer was separated, and the aq. layer was extracted with hexane. The combined organic phase was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by silica-gel column chromatography to give **2a** (0.36 g, 96% yield) as a pale yellow viscous oil. R_f 0.78 (hexane–dichloromethane = 1 : 1). ^1H NMR (200 MHz, CDCl_3) δ = 0.52–0.76 (m, 6H), 0.89–1.03 (m, 9H), 6.04 (brs, 1H), 7.48–7.62 (m, 3H), 7.85–8.13 (m, 4H); ^{19}F NMR (188 MHz, CDCl_3) δ = –58.9; IR (neat) 2957, 2912, 2878, 1599, 1512, 1458, 1412, 1379, 1334, 1280, 1234, 1174, 1134, 1082, 1041, 1022, 1005, 931, 873, 844, 812, 790, 771, 731 cm^{-1} ; MS m/z (rel intensity) 464 (M^+ +4, 0.8), 462 (M^+ +2, 1), 460 (M^+ , 0.8), 302 (25), 271 (100), 167 (69), 140 (55), 127 (31), 77 (86). HRMS Found: m/z 459.9877. Calcd for $\text{C}_{18}\text{H}_{23}\text{Br}_2\text{FOSi}$: M, 459.9869.

1,1-Dibromo-2-*t*-butyldimethylsilyloxy-1-fluoro-2-(1-naphthyl)ethane (2b)

A 50-ml two-necked round-bottomed flask was charged with 2,2-dibromo-2-fluoro-1-(naphthyl)ethanol (0.97 g, 2.8 mmol) and dichloromethane (10 ml) under an argon atmosphere and cooled at 0 °C. To the flask were added 2,6-lutidine (7.0 ml, 6.0 mmol) and *t*-butyldimethylsilyl trifluoromethanesulfonate (1.05 ml, 9.0 mmol) at 0 °C. The reaction mixture was stirred for 5 h at room temperature and then neutralized with sat. Na_2CO_3 aq. solution (5 ml). The organic layer was separated, and the aq. layer was extracted with dichloromethane. The combined organic phase was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by silica-gel column chromatography to give **2b** (1.06 g, 82%) as a pale yellow oil. R_f 0.79 (hexane–dichloromethane = 1 : 1). ^1H NMR (200 MHz, CDCl_3) δ = –0.18 (s, 3H), 0.23 (s, 3H), 0.98 (s, 9H), 6.0 (d, J = 4.8 Hz, 1H), 7.5 (m, 3H), 7.90 (m, 2H), 8.10 (m, 2H); ^{13}C NMR (50 MHz, CDCl_3) δ = –4.8, –4.4, 18.4, 25.9, 78.3 (d, J = 24.4 Hz), 103.8 (d, J = 326.0 Hz), 123.1, 125.1, 125.7, 126.7, 128.0, 129.2, 130.0, 131.7, 133.1, 133.6; ^{19}F NMR (188 MHz, CDCl_3) δ = –18.8 (d, J = 4.8 Hz); IR (neat) 2955, 2930, 2858, 1599, 1512, 1471, 1462, 1399, 1361, 1334, 1280, 1253, 1172, 1132,

1041, 1024, 1005, 933, 877, 839, 777, 717 cm^{-1} ; MS m/z (rel intensity) 466 (M^+ +6, 0.03), 465 (M^+ +5, 0.1), 464 (M^+ +4, 0.4), 463 (M^+ +3, 0.2), 462 (M^+ +2, 0.8), 461 (M^+ +1, 0.09), 460 (M^+ , 0.3), 302 (0.5), 271 (29), 245 (16), 167 (100), 140 (19), 127 (10), 77 (24). Found: C, 46.89; H, 4.89%. Calcd for $\text{C}_{18}\text{H}_{23}\text{Br}_2\text{FOSi}$: C, 46.77; H, 5.02%.

1,1-Dibromo-1-fluoro-2-methoxy-2-(1-naphthyl)ethane (2c)

A 50 ml two-necked round-bottomed flask was charged with NaH (60% in oil, 0.080 g, 2.0 mmol) and THF (4 ml), filled with argon and cooled to 0 °C. To the flask were added a solution of 2,2-dibromo-2-fluoro-1-(naphthyl)ethanol (0.52 g, 1.5 mmol) in THF (4 ml) and methyl iodide (0.19 ml, 3.0 mmol) at 0 °C. The reaction mixture was stirred for 3 h at 0 °C and for 1 h at room temperature and then treated with sat. NH_4Cl aq. solution (5 ml). The organic layer was separated and the aq. layer was extracted with diethyl ether. The combined organic phase was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by silica-gel column chromatography to give **2c** (0.26 g, 47% yield) as a brown oil. R_f 0.59 (hexane–ethyl acetate = 5 : 1). ^1H NMR (200 MHz, CDCl_3) δ = 3.49 (s, 3H), 5.52 (d, J = 7.6 Hz, 1H), 7.56 (m, 3H), 7.91 (m, 3H), 8.13 (m, 1H); ^{13}C NMR (50 MHz, CDCl_3) δ = 58.5, 87.1 (d, J = 23.6 Hz), 99.8 (d, J = 321.9 Hz), 123.6 (d, J = 3.8 Hz), 125.3, 125.9, 126.8, 127.7, 129.2, 129.8, 130.4, 132.7, 133.9; ^{19}F NMR (188 MHz, CDCl_3) δ = –59.7 (d, J = 6.8 Hz); IR (neat) 3070, 2932, 2829, 1597, 1512, 1450, 1396, 1333, 1286, 1230, 1199, 1167, 1120, 1101, 1051, 1026, 997, 974, 931, 875, 819, 796, 773, 721 cm^{-1} ; MS m/z (rel intensity) 365 (M^+ +5, 0.5), 364 (M^+ +4, 3), 363 (M^+ +3, 0.9), 362 (M^+ +2, 6), 361 (M^+ +1, 0.5), 360 (M^+ , 3), 282 (0.2), 202 (12), 171 (100), 127 (32). Found: C, 43.22; H, 3.10%. Calcd for $\text{C}_{13}\text{H}_{11}\text{Br}_2\text{FO}$: C, 43.13; H, 3.06%.

1,1-Dibromo-1-fluoro-2-(methoxy)methoxy-2-(1-naphthyl)ethane (2d)

A 50 ml two-necked round-bottomed flask was charged with NaH (60% in oil, 0.072 g, 1.8 mmol) and THF (3 ml) under an argon atmosphere and cooled to 0 °C. To the flask were added a solution of 2,2-dibromo-2-fluoro-1-(naphthyl)ethanol (0.42 g, 1.2 mmol) in THF (3 ml) and chloromethyl methyl ether (140 ml, 1.8 mmol). The reaction mixture was stirred for 1 h at 0 °C and for 0.5 h at room temperature. Workup followed by purification by column chromatography gave **2d** (0.33 g, 70% yield). R_f 0.65 (hexane–dichloromethane = 1 : 1). ^1H NMR (200 MHz, CDCl_3) δ = 3.44 (s, 3H), 4.61 (d, J = 6.9 Hz, 1H), 4.80 (d, J = 6.9 Hz, 1H), 6.00 (d, J = 9.2 Hz, 1H), 7.53 (m, 3H), 7.90 (m, 3H), 8.14 (m, 1H); ^{13}C NMR (50 MHz, CDCl_3) δ = 56.8, 80.0, 95.2, 99.6 (J

= 323 Hz), 123.5, 124.9, 125.7, 126.6, 127.8, 130.0, 130.2, 132.4, 133.5; ^{19}F NMR (188 MHz, CDCl_3) δ = -59.4 (d, J = 6.8 Hz); IR (neat) 3053, 2957, 2895, 2843, 2826, 1952, 1597, 1512, 1464, 1441, 1396, 1340, 1288, 1265, 1232, 1215, 1153, 1107, 1050, 922, 873, 821, 773, 735 cm^{-1} ; MS m/z (rel intensity) 394 (M^+ +4, 3), 392 (M^+ +2, 6), 390 (M^+ , 3), 314 (1), 312 (1), 232 (15), 201 (95), 170 (100), 159 (79), 141 (98), 127 (92), 85 (90), 63 (57). Found: C, 42.82; H, 3.31%. Calcd for $\text{C}_{14}\text{H}_{13}\text{Br}_2\text{FO}_2$: C, 42.89; H, 3.34%.

1,1-Dibromo-1-fluoro-2-(2-methoxyethoxy)methoxy-2-(1-naphthyl)ethane (2e)

A solution of 2,2-dibromo-2-fluoro-1-(naphthyl)ethanol (1.01 g, 2.9 mmol) in THF (5 ml) and successively chloromethyl 2-methoxyethyl ether (0.41 ml, 3.6 mmol) were added to NaH (60% in oil, 0.14 g, 3.6 mmol) in THF (5 ml) at 0 °C under an argon atmosphere. Workup and purification by column chromatography gave **2e** (1.09 g, 86% yield) as a pale yellow oil. R_f 0.29 (hexane–dichloromethane = 1 : 4). ^1H NMR (200 MHz, CDCl_3) δ = 3.27 (s, 3H), 3.29–3.60 (m, 3H), 3.92–4.01 (m, 1H), 4.70 (d, J = 7.0 Hz, 1H), 4.95 (d, J = 7.0 Hz, 1H), 6.03 (d, J = 9.4 Hz, 1H), 7.36 (m, 3H), 7.89 (m, 3H), 8.15 (d, J = 8.0 Hz, 1H); ^{13}C NMR (50 MHz, CDCl_3) δ = 58.9, 67.9, 71.4, 85.4 (d, J = 21.5 Hz), 94.2, 99.6 (d, J = 322.7 Hz), 123.6, 124.9, 125.8, 126.6, 127.9, 128.4, 128.9, 130.2, 132.3, 133.6; ^{19}F NMR (188 MHz, CDCl_3) δ = -59.4 (d, J = 7.8 Hz); IR (neat) 3053, 2926, 2893, 1597, 1512, 1452, 1396, 1367, 1288, 1240, 1199, 1176, 1116, 1055, 987, 931, 852, 821, 798, 775, 723 cm^{-1} ; MS m/z (rel intensity) 436 (M^+ +2, 0.6), 252 (4), 250 (15), 170 (63), 127 (31), 89 (100). Found: C, 43.78; H, 3.94%. Calcd for $\text{C}_{16}\text{H}_{17}\text{Br}_2\text{FO}_3$: C, 44.07; H, 3.93%.

1,1-Dibromo-1-fluoro-2-(2-methoxyethoxy)methoxy-2-phenylethane (2f): Obtained in 78% yield, according to the procedure described above. A pale yellow oil, R_f 0.28 (hexane–ethyl acetate = 5 : 1). ^1H NMR (200 MHz, CDCl_3) δ = 3.33 (s, 3H), 3.36–3.64 (m, 3H), 3.80–3.98 (m, 1H), 4.73 (d, J = 7.0 Hz, 1H), 4.91 (d, J = 7.0 Hz, 1H), 5.13 (d, J = 10.3 Hz, 1H), 7.31–7.55 (m, 5H); ^{13}C NMR (50 MHz, CDCl_3) δ = 59.0, 67.9, 71.5, 85.5 (d, J = 22.1 Hz), 94.2, 99.4 (d, J = 321.6 Hz), 128.2, 129.5, 129.6 (d, J = 1.5 Hz), 134.0 (d, J = 0.76 Hz); ^{19}F NMR (188 MHz, CDCl_3) δ = -61.3 (d, J = 10.2 Hz); IR (neat) 3065, 3034, 2926, 2893, 2818, 1495, 1454, 1405, 1367, 1279, 1242, 1199, 1172, 1118, 1057, 974, 937, 790, 758, 735, 700 cm^{-1} ; MS m/z (rel intensity) 388 (M^+ +4, 3), 386 (M^+ +2, 9), 384 (M^+ , 3), 307 (13), 226 (15), 155 (15), 105 (22), 89 (51), 82 (100). HRMS Found: m/z 383.9400. Calcd for $\text{C}_{12}\text{H}_{15}\text{Br}_2\text{FO}_3$: M, 383.9372.

1,1-Dibromo-1-fluoro-2-(2-methoxyethoxy)methoxy-4-phenylbutane (2g):

This was isolated in 81% yield as a pale yellow oil, R_f 0.32 (hexane–dichloromethane = 1 : 5). ^1H NMR (200 MHz, CDCl_3) δ = 1.94–2.36 (m, 2H), 2.67–3.03 (m, 2H), 3.84 (s, 3H), 3.55–3.59 (m, 2H), 3.70–3.87 (m, 1H), 3.90–3.98 (m, 2H), 4.90 (d, J = 7.0 Hz, 1H), 4.98 (d, J = 7.0 Hz, 1H), 7.18–7.34 (m, 5H); ^{13}C NMR (50 MHz, CDCl_3) δ = 31.6, 34.5 (d, J = 1.5 Hz), 59.2, 68.4, 71.7, 85.9 (d, J = 17.9 Hz), 97.3 (d, J = 3.4 Hz), 102.3 (d, J = 321.6 Hz), 126.4, 128.6, 128.7, 141.0; ^{19}F NMR (188 MHz, CDCl_3) δ = -56.5 (d, J = 6.8 Hz); IR (neat) 3063, 3028, 2930, 2818, 1603, 1496, 1454, 1365, 1286, 1244, 1197, 1116, 1012, 935, 850, 785, 752, 700 cm^{-1} ; MS m/z (rel intensity) 340 (3), 338 (5), 336 (3), 229 (2), 227 (2), 147 (91), 129 (18), 89 (100), 77 (22). Found: C, 40.48; H, 4.48%. Calcd for $\text{C}_{14}\text{H}_{19}\text{Br}_2\text{FO}_3$: C, 40.61; H, 4.62%.

1,1-Dibromo-2-cyclohexyl-1-fluoro-2-(2-methoxyethoxy)methoxyethane (2h):

This product was obtained in 71% yield as a pale yellow oil, R_f 0.30 (hexane–dichloromethane = 1 : 5). ^1H NMR (200 MHz, CDCl_3) δ = 1.11–2.04 (m, 11H), 3.39 (s, 3H), 3.57 (t, J = 4.7 Hz, 2H), 3.70–3.80 (m, 2H), 3.89 (dt, J = 4.7, 11.0 Hz, 1H), 4.93 (s 2H); ^{13}C NMR (50 MHz, CDCl_3) δ = 26.4, 26.8, 27.7 (d, J = 1.5 Hz), 32.6 (d, J = 1.1 Hz), 40.8 (d, J = 0.77 Hz), 59.3, 68.6 (d, J = 0.76 Hz), 71.8, 90.3 (d, J = 17.5 Hz), 98.1 (d, J = 1.9 Hz), 101.9 (d, J = 325.0 Hz); ^{19}F NMR (188 MHz, CDCl_3) δ = -54.8 (d, J = 10.2 Hz); IR (neat) 2928, 2855, 1450, 1242, 1199, 1172, 1120, 1099, 1020, 976, 846, 781, 748 cm^{-1} ; MS m/z (rel intensity) 289 (0.3), 287 (0.7), 285 (0.5), 207 (10), 205 (10), 125 (22), 105 (47), 83 (45), 60 (100). Found: C, 36.79; H, 5.60%. Calcd for $\text{C}_{12}\text{H}_{21}\text{Br}_2\text{FO}_3$: C, 36.76; H, 5.40%.

1,1-Dibromo-1-fluoro-2-(2-methoxyethoxy)methoxy-3-methylbutane (2i):

This compound was prepared in 56% yield as a pale yellow oil, R_f 0.37 (hexane–ethyl acetate = 5 : 1). ^1H NMR (200 MHz, CDCl_3) δ = 1.09 (t, J = 7.4 Hz, 6H), 2.37 (d, J = 2.3 Hz, 1H), 3.39 (s, 3H), 3.39–3.59 (m, 2H), 3.69–3.94 (m, 3H), 4.96 (dd, J = 7.0, 10.7 Hz, 2H); ^{13}C NMR (50 MHz, CDCl_3) δ = 17.1 (d, J = 1.9 Hz), 22.1, 30.6, 59.1, 68.4, 71.7, 90.3 (d, J = 17.9 Hz), 98.0, 101.7 (d, J = 325.4 Hz); ^{19}F NMR (188 MHz, CDCl_3) δ = -55.3 (d, J = 11.5 Hz); IR (neat) 2968, 2880, 2818, 1469, 1388, 1367, 1280, 1242, 1199, 1176, 1035, 980, 906, 852, 783, 744 cm^{-1} ; MS m/z (rel intensity) 279 (0.9), 277 (2), 275 (0.7), 249 (3), 247 (6), 245 (3), 167 (18), 165 (16), 105 (41), 89 (63), 87 (37), 61 (100). Found: C, 30.83; H, 5.02%. Calcd for $\text{C}_9\text{H}_{17}\text{Br}_2\text{FO}_3$: C, 30.71; H, 4.87%.

1,1-Dibromo-1-fluoro-2-methoxyethoxymethoxy-3-methyl-3-phenylpropane (2j):

Obtained in 60% yield as a pale yellow oil, R_f 0.30 (hexane–ethyl

acetate = 5 : 1). ^1H NMR (200 MHz, CDCl_3) *syn* isomer: δ = 1.46 (dd, J = 1.0, 7.2 Hz, 3H), 3.35 (s, 3H), 3.41–3.47 (m, 2H), 3.48–3.55 (md, J = 3.9 Hz, 1H), 3.64–3.71 (m, 2H), 4.20 (dd, J = 3.9, 10.2 Hz, 2H), 4.71 (d, J = 6.8 Hz, 1H), 4.84 (d, J = 6.8 Hz, 1H), 7.18–7.35 (m, 5H). *anti* isomer: 3.35 (s, 3H), 4.06 (dd, J = 5.7, 7.8 Hz, 1H); ^{13}C NMR (50 MHz, CDCl_3) δ = 15.9, 41.7 (d, J = 1.2 Hz), 59.1, 68.5, 71.6, 89.4 (d, J = 17.5 Hz), 97.8 (d, J = 1.1 Hz), 126.9, 127.8, 128.7, 144.3; ^{19}F NMR (188 MHz, CDCl_3) *anti* isomer: δ = –53.5 (d, J = 10.3 Hz), *syn* isomer: δ = –52.0 (d, J = 8.1 Hz); IR (neat) 2982, 2932, 2882, 1603, 1495, 1454, 1410, 1244, 1199, 1174, 1116, 1064, 1041, 850, 765, 735, 702 cm^{-1} ; MS m/z (rel intensity) 310 (1), 308 (3), 306 (1), 229 (31), 227 (29), 147 (29), 133 (59), 118 (9), 105 (97), 89 (100), 77 (66).

General Procedure for Diastereoselective Generation and Carbonyl Addition of RCH(OR')CFBrLi (3)

A hexane solution of butyllithium (1.62 M, 0.30 ml, 0.48 mmol) was added to a solution of **2** (0.40 mmol) and 4-heptanone (120 ml, 0.80 mmol) in THF (3 ml) and diethyl ether (1.5 ml) at –130 °C via a syringe over a period of 10 min. The resulting mixture was stirred for 1 h at –130 °C and warmed up to –78 °C before quenching with sat. aq. NH_4Cl solution. The aq. layer was extracted with diethyl ether (20 ml x 5). The combined extracts were dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by silica-gel column chromatography to afford the adduct.

2-Bromo-2-fluoro-1-(1-naphthyl)-3-propyl-1-triethylsiloxy-3-hexanol

(**4a**): This silyl adduct was obtained in 31% yield as a 57 : 25 mixture of diastereomers. A colorless oil, R_f 0.26 (hexane–dichloromethane = 2 : 1). ^1H NMR (200 MHz, CDCl_3) *syn*-isomer: δ = 0.23–0.55 (m, 6H), 0.72–0.89 (m, 9H), 0.91–1.08 (m, 6H), 1.42–1.65 (m, 4H), 1.76–2.13 (m, 4H), 3.28 (s, 1H), 6.23 (s, 1H), 7.42–7.58 (m, 3H), 7.85–8.13 (m, 4H), *anti*-isomer: δ = 6.34 (d, J = 23.5 Hz, 1H); ^{13}C NMR (50 MHz, CDCl_3) δ = 5.2, 6.8, 14.9 (d, J = 0.76 Hz), 15.1, 17.2 (d, J = 3.1 Hz), 17.7 (d, J = 2.6 Hz), 38.1, 38.5, 70.8 (d, J = 33.2 Hz), 80.4 (d, J = 20.9 Hz), 122.6 (d, J = 4.2 Hz), 123.1 (d, J = 260.7 Hz), 124.5, 125.3, 126.4, 129.05, 129.11, 129.5, 131.9 (d, J = 1.9 Hz), 133.4, 134.7; ^{19}F NMR (188 MHz, CDCl_3) *syn*-isomer: δ = –113.2, *anti*-isomer: δ = –132.0 (d, J = 23.7 Hz); IR (neat) 3497, 3053, 2961, 2876, 1599, 1512, 1458, 1412, 1379, 1299, 1236, 1172, 1118, 1072, 1003, 970, 879, 858, 808, 775, 744 cm^{-1} ; MS m/z (rel intensity) 323 (2), 321 (2), 302 (3), 271 (85), 227 (3), 225 (2), 213 (4), 141 (11), 127 (4), 115 (24), 43 (100). Found: C, 59.56; H, 7.62%. Calcd for $\text{C}_{25}\text{H}_{38}\text{BrFO}_2\text{Si}$: C, 60.35; H, 7.70%.

(1*R**, 2*S**)-(±)-2,3-Epoxy-2-fluoro-1-(1-naphthyl)-3-propyl-1-triethylsilyloxy-hexane (**5a**):

This epoxide accompanied in 7% yield as a colorless oil, R_f 0.43 (hexane–dichloromethane = 2 : 1). ^1H NMR (200 MHz, CDCl_3) δ = 0.54–0.67 (m, 6H), 0.76–0.94 (m, 15H), 1.23–1.41 (m, 4H), 1.45–1.62 (m, 3H), 1.69–1.85 (m, 1H), 5.79 (d, J = 17.2 Hz, 1H), 7.41–7.57 (m, 3H), 7.71–7.87 (m, 3H), 8.16 (d, J = 7.8 Hz, 1H); ^{13}C NMR (50 MHz, CDCl_3) δ = 4.9, 6.8, 14.1, 14.4, 18.2 (d, J = 1.5 Hz), 18.2, 32.0 (d, J = 1.1 Hz), 32.3 (d, J = 2.6 Hz), 70.8 (d, J = 19.1 Hz), 72.6 (d, J = 35.5 Hz), 102.5 (d, J = 270.5 Hz), 124.2 (d, J = 2.7 Hz), 125.2, 125.6 (d, J = 2.7 Hz), 125.7, 126.0, 128.87, 128.94, 131.2; ^{19}F NMR (188 MHz, CDCl_3) δ = –138.1 (d, J = 16.9 Hz); IR (neat) 3053, 2961, 2876, 1599, 1512, 1466, 1414, 1379, 1238, 1169, 1113, 1005, 951, 848, 790, 744 cm^{-1} ; MS m/z (rel intensity) 271 (100), 213 (7), 141 (28), 127 (6), 115 (35). Found: C, 71.99; H, 9.03%. Calcd for $\text{C}_{25}\text{H}_{37}\text{FO}_2\text{Si}$: C, 72.07; H, 8.95%.

(1*R**, 2*S**)-(±)-2-Bromo-1-*t*-butyldimethylsilyloxy-2-fluoro-1-(1-naphthyl)-3-propyl-3-hexanol (**4b**):

Obtained in 34% yield as a colorless oil, R_f 0.35 (hexane–dichloromethane = 2 : 1). ^1H NMR (200 MHz, CDCl_3) δ = –0.51 (s, 3H), 0.12 (s, 3H), 0.86–1.06 (m, 6H), 0.96 (s, 9H), 1.39–1.62 (m, 4H), 1.79–2.07 (m, 4H), 3.09 (s, 1H), 6.20 (s, 1H), 7.43–7.58 (m, 3H), 7.84–7.98 (m, 2H), 8.01–8.09 (m, 2H); ^{13}C NMR (50 MHz, CDCl_3) δ = –4.4, –3.6, 15.0 (d, J = 1.1 Hz), 15.1 (d, J = 0.8 Hz), 17.2 (d, J = 4.1 Hz), 17.7 (d, J = 2.7 Hz), 18.2, 26.1, 38.1, 38.7, 70.0 (d, J = 32.8 Hz), 80.5 (d, J = 21.4 Hz), 122.6 (d, J = 3.8 Hz), 123.22 (d, J = 262.1 Hz), 124.6, 125.3, 126.5, 129.2, 129.4, 132.0, 133.4, 134.0, 134.7; ^{19}F NMR (188 MHz, CDCl_3) δ = –113.1; IR (neat) 3510, 3053, 2961, 2859, 1599, 1512, 1464, 1390, 1361, 1336, 1286, 1255, 1232, 1170, 1120, 1070, 1005, 968, 839, 777, 735 cm^{-1} ; MS m/z (rel intensity) 498 (M^+ +2, 11), 496 (M^+ , 8), 477 (18), 350 (10), 300 (16), 271 (10), 156 (10), 115 (26), 81 (81), 79 (30), 69 (100). Found: C, 60.63; H, 7.69%. Calcd for $\text{C}_{25}\text{H}_{38}\text{FBrO}_2\text{Si}$: C, 60.35; H, 7.70%.

(1*R**, 2*S**)-(±)-1-*t*-Butyldimethylsilyloxy-2,3-epoxy-2-fluoro-1-(1-naphthyl)-3-propylhexane (**5b**):

As a byproduct of **4b**, this epoxide formed in 13% yield as a colorless oil, R_f 0.56 (hexane–dichloromethane = 2 : 1). ^1H NMR (200 MHz, CDCl_3) δ = –0.02 (s, 3H), 0.15 (s, 3H), 0.75–0.92 (m, 6H), 0.92 (s, 9H), 1.18–1.43 (m, 4H), 1.46–1.82 (m, 4H), 5.79 (d, J = 21.0 Hz, 1H), 7.42–7.57 (m, 3H), 7.71–7.88 (m, 3H), 8.13–8.17 (m, 1H); ^{13}C NMR (50 MHz, CDCl_3) δ = –4.8, –4.6 (d, J = 0.7 Hz), 14.1, 14.3, 18.1 (d, J = 1.5 Hz), 18.3, 18.5, 26.0, 32.1 (d, J = 0.76 Hz), 32.3 (d, J = 2.7 Hz), 70.7 (d, J = 18.7 Hz), 73.1 (d, J = 34.7 Hz), 102.6 (d, J = 296.0 Hz), 124.3 (d, J = 2.6 Hz), 125.1, 125.5 (d, J = 2.6 Hz), 125.7, 126.0, 128.9 (d, J =

3.4 Hz), 131.2, 133.9, 135.3, 135.4; ^{19}F NMR (188 MHz, CDCl_3) $\delta = -137.8$ (d, $J = 21.0$ Hz); IR (neat) 3053, 2961, 2932, 2858, 1599, 1512, 1460, 1361, 1253, 1169, 1113, 1005, 951, 868, 839, 779 cm^{-1} ; MS m/z (rel intensity) 416 (M^+ , 0.1), 359 (2), 339 (5), 271 (52), 233 (99), 213 (9), 155 (20), 141 (18), 127 (8), 77 (76), 73 (100). HRMS Found: m/z 416.2571. Calcd for $\text{C}_{25}\text{H}_{37}\text{FO}_2\text{Si}$: M, 416.2547.

2-Bromo-2-fluoro-1-methoxy-1-(1-naphthyl)-3-propyl-3-hexanol (4c):

Isolated in 49% yield as a 60 : 40 mixture of diastereomers, a pale yellow oil, R_f 0.22 (hexane–diethyl ether = 5 : 1). ^1H NMR (200 MHz, CDCl_3) $\delta = 0.89$ – 1.09 (m, 6H), 1.26 – 2.05 (m, 8H), 3.31 (s, 3H), 5.68 (s, 1H), 7.43 – 7.68 (m, 3H), 7.87 – 7.90 (m, 4H); ^{19}F NMR (188 MHz, CDCl_3) *syn*-isomer: $\delta = -113.8$, *anti*-isomer: $\delta = -131.8$ (d, $J = 23.7$ Hz); IR (neat) 3491, 3051, 2963, 2934, 2874, 2361, 1597, 1512, 1466, 1398, 1294, 1232, 1197, 1169, 1099, 1072, 1032, 1001, 964, 910, 798, 777, 735 cm^{-1} ; MS m/z (rel intensity) 398 ($\text{M}^+ + 2$, 0.4), 396 (M^+ , 0.5), 252 (3), 250 (3), 243 (1), 241 (1), 202 (1), 171 (100), 128 (9), 115 (4). HRMS Found: m/z 396.1072. Calcd for $\text{C}_{20}\text{H}_{26}\text{BrFO}_2$: M, 396.1101.

2-Bromo-2-fluoro-1-methoxymethoxy-1-(1-naphthyl)-3-propyl-3-hexanol (4d):

Obtained in 55% yield as a 85 : 15 mixture of diastereomers, a pale yellow oil, R_f 0.25 (hexane–diethyl ether = 5 : 1). ^1H NMR (200 MHz, CDCl_3) *syn*-isomer: $\delta = 0.90$ – 1.10 (m, 6H), 1.25 – 1.68 (m, 4H), 1.90 – 2.12 (m, 4H), 3.30 (s, 1H), 3.46 (s, 3H), 4.58 (d, $J = 6.7$ Hz, 1H), 4.66 (dd, $J = 1.8, 6.7$ Hz, 1H), 6.26 (s, 1H), 7.44 – 7.62 (m, 3H), 7.86 – 8.01 (m, 4H), *anti*-isomer: $\delta = 6.38$ (d, $J = 22.0$ Hz, 1H); ^{13}C NMR (50 MHz, CDCl_3) $\delta = 15.0$ (d, $J = 0.76$ Hz), 15.1 , 17.2 (d, $J = 3.4$ Hz), 17.7 (d, $J = 2.3$ Hz), 37.4 , 38.7 , 57.7 , 73.6 (d, $J = 32.1$ Hz), 80.5 (d, $J = 20.9$ Hz), 95.0 , 121.5 (d, $J = 261.7$ Hz), 123.1 (d, $J = 4.6$ Hz), 124.9 , 125.6 , 126.5 , 128.3 , 129.0 , 129.7 , 131.3 , 133.0 , 133.6 ; ^{19}F NMR (188 MHz, CDCl_3) *syn*-isomer: $\delta = -113.0$, *anti*-isomer: $\delta = -130.6$ (d, $J = 22.0$ Hz); IR (neat) 3503, 3053, 2963, 2874, 2828, 1597, 1512, 1466, 1379, 1292, 1265, 1234, 1213, 1157, 1045, 922, 856, 798, 777, 738 cm^{-1} ; MS m/z (rel intensity) 428 ($\text{M}^+ + 2$, 2), 426 (M^+ , 2), 252 (16), 250 (16), 201 (100), 171 (17), 169 (41), 141 (44). HRMS Found: m/z 426.1191. Calcd for $\text{C}_{21}\text{H}_{28}\text{BrFO}_3$: M, 426.1205.

2-Bromo-2-fluoro-1-(2-methoxyethoxy)methoxy-1-(1-naphthyl)-3-propyl-3-hexanol (4e):

Prepared in 55% yield as a 83 : 17 mixture of diastereomers, a pale yellow oil, R_f 0.12 (hexane–diethyl ether = 5 : 1). ^1H NMR (200 MHz, CDCl_3) *syn*-isomer: $\delta = 0.88$ – 1.07 (m, 6H), 1.42 – 1.61 (m, 4H), 1.92 – 2.06 (m, 4H), 3.32 (s, 3H), 3.35 – 3.65 (m, 3H), 3.76 – 3.94 (m, 1H), 4.62 (d, $J = 6.9$ Hz, 1H), 4.79 (dd, $J = 1.8, 6.9$ Hz, 1H), 6.27 (s, 1H), 7.41 – 7.59 (m, 3H), 7.84 – 8.18 (m, 4H), *anti*-isomer: $\delta = 3.30$ (s, 3H), 4.39 (d, $J = 6.8$ Hz, 1H), 4.67 (d, $J = 6.8$ Hz, 1H), 6.37 (d, $J = 23.7$

Hz, 1H); ^{13}C NMR (50 MHz, CDCl_3) $\delta = 14.9$, 15.0 , 17.0 (d, $J = 3.1$ Hz), 17.6 (d, $J = 2.3$ Hz), 37.4 , 38.6 , 58.9 , 69.0 , 71.6 , 73.2 (d, $J = 32.4$ Hz), 80.3 (d, $J = 21.0$ Hz), 93.6 , 121.4 (d, $J = 261.7$ Hz), 123.2 (d, $J = 4.2$ Hz), 124.7 , 125.4 , 126.3 , 128.1 , 128.8 , 129.4 , 131.4 , 132.9 , 133.4 ; ^{19}F NMR (188 MHz, CDCl_3) *syn*-isomer: $\delta = -112.7$, *anti*-isomer: $\delta = -130.0$ (d, $J = 23.7$ Hz); IR (neat) 3497, 3053, 2963, 2874, 1597, 1512, 1456, 1396, 1294, 1234, 1199, 1174, 1045, 925, 912, 854, 798, 777, 738 cm^{-1} ; MS m/z (rel intensity) 472 ($\text{M}^+ + 2$, 0.4), 470 (M^+ , 0.4), 351 (0.3), 250 (13), 245 (15), 225 (2), 199 (1), 183 (3), 171 (12), 156 (8), 128 (6), 115 (10), 89 (100), 71 (16). HRMS Found: m/z 470.1469. Calcd for $\text{C}_{23}\text{H}_{32}\text{BrFO}_4$: M, 470.1468.

2-Bromo-2-fluoro-1-(2-methoxyethoxy)methoxy-1-phenyl-3-propyl-3-hexanol (4f):

This adduct was obtained in 58% yield as a 50 : 50 mixture of diastereomers, a pale yellow oil, R_f 0.15 (hexane–diethyl ether = 5 : 1). ^1H NMR (200 MHz, CDCl_3) *syn*-isomer: $\delta = 0.87$ – 1.02 (m, 6H), 1.42 – 1.78 (m, 4H), 1.80 – 1.97 (m, 4H), 3.34 (s, 3H), 3.38 – 3.68 (m, 4H), 3.77 – 3.96 (m, 1H), 4.52 (d, $J = 7.0$ Hz, 1H), 4.69 (d, $J = 7.0$ Hz, 1H), 5.26 (s, 1H), 7.34 – 7.54 (m, 5H), *anti*-isomer: $\delta = 3.35$ (s, 3H), 4.69 (d, $J = 7.0$ Hz, 1H), 4.81 (dd, $J = 1.9, 7.0$ Hz, 1H), 5.29 (d, $J = 23.1$ Hz, 1H); ^{13}C NMR (50 MHz, CDCl_3) one isomer: $\delta = 14.9$ (d, $J = 0.77$ Hz), 14.6 (d, $J = 0.76$ Hz), 16.7 (d, $J = 2.6$ Hz), 17.2 (d, $J = 2.6$ Hz), 37.5 , 38.2 , 59.1 , 68.9 , 71.7 , 79.5 (d, $J = 31.5$ Hz), 79.9 (d, $J = 21.4$ Hz), 93.7 , 120.2 (d, $J = 261.7$ Hz), 128.0 , 129.1 , 130.7 (d, $J = 1.3$ Hz), 135.2 , the other isomer: $\delta = 15.06$, 15.09 , 17.3 , 17.7 (d, $J = 3.1$ Hz), 59.1 , 69.2 , 71.8 , 80.5 (d, $J = 19.1$ Hz), 82.7 (d, $J = 20.6$ Hz), 93.9 , 127.8 , 129.0 , 129.7 (d, $J = 1.9$ Hz), 135.0 (d, $J = 1.5$ Hz); ^{19}F NMR (188 MHz, CDCl_3) *syn*-isomer: $\delta = -113.9$ (s), *anti*-isomer: $\delta = -127.5$ (d, $J = 23.7$ Hz); IR (neat) 3500, 2963, 2874, 1506, 1456, 1400, 1300, 1242, 1201, 1172, 1113, 1070, 1024, 850, 736, 702 cm^{-1} ; MS m/z (rel intensity) 423 ($\text{M}^+ + 2$, 0.5), 421 (M^+ , 0.6), 342 (0.6), 307 (1), 305 (0.8), 200 (16), 195 (6), 164 (3), 105 (7), 89 (100). HRMS Found: m/z 421.1375. Calcd for $\text{C}_{19}\text{H}_{31}\text{BrFO}_4$: M, 421.1390.

4-Bromo-4-fluoro-3-(2-methoxyethoxy)methoxy-1-phenyl-5-propyl-5-octanol (4g):

This product was isolated in 62% yield as a 62 : 38 mixture of diastereomers, a pale yellow oil, R_f 0.14 (hexane–diethyl ether = 4 : 1). ^1H NMR (200 MHz, CDCl_3) *syn*-isomer: $\delta = 0.84$ – 0.97 (m, 6H), 1.21 – 1.46 (m, 4H), 1.59 – 1.87 (m, 4H), 2.11 – 2.40 (m, 1H), 2.73 – 2.83 (m, 3H), 2.87 (s, 1H), 3.38 (s, 3H), 3.53 – 3.58 (m, 2H), 3.74 – 3.79 (m, 2H), 4.02 – 4.09 (m, 1H), 4.86 (d, $J = 6.9$ Hz, 1H), 4.90 (d, $J = 8.2$ Hz, 1H), 7.19 – 7.34 (m, 5H), *anti*-isomer: $\delta = 0.73$ (t, $J = 6.8$ Hz, 3H), 0.92 (t, $J = 7.2$ Hz, 3H), 3.40 (s, 3H), 4.91 (s, 2H); ^{19}F NMR (188 MHz, CDCl_3) *syn*-isomer: $\delta = -112.3$ (s), *anti*-isomer: $\delta = -107.1$ (d, $J = 6.8$ Hz); IR (neat) 3460, 3026, 2963,

2874, 2249, 1948, 1603, 1496, 1456, 1363, 1294, 1199, 1157, 1033, 910, 860 cm^{-1} ; MS m/z (rel intensity) 450 ($M^+ + 2$, 0.1), 448 (M^+ , 0.1), 275 (8), 223 (1), 210 (5), 208 (5), 147 (39), 115 (45), 91 (79), 89 (100). HRMS Found: m/z 448.1610. Calcd for $\text{C}_{21}\text{H}_{34}\text{BrFO}_4$: M, 448.1624.

2-Bromo-1-cyclohexyl-2-fluoro-1-(2-methoxyethoxy)methoxy-3-propyl-3-hexanol (4h): This alcohol was isolated in 51% yield as a 92 : 8 mixture of diastereomers, a colorless oil, R_f 0.20 (hexane-ethyl acetate = 3 : 1). ^1H NMR (200 MHz, CDCl_3) δ = 0.89–0.98 (m, 6H), 1.10–1.48 (m, 10H), 1.60–1.89 (m, 8H), 2.03–2.89 (m, 2H), 3.08 (s, 1H), 3.38 (s, 3H), 3.39–3.67 (m, 2H), 3.70–3.86 (m, 3H), 4.86 (d, J = 6.4 Hz, 1H), 4.90 (dd, J = 1.4, 6.4 Hz, 1H); ^{13}C NMR (50 MHz, CDCl_3) δ = 14.8 (d, J = 0.8 Hz), 15.0 (d, J = 0.8 Hz), 16.7 (d, J = 3.1 Hz), 17.5 (d, J = 3.4 Hz), 26.5, 26.6, 26.9, 29.0 (d, J = 1.2 Hz), 33.9 (d, J = 3.1 Hz), 37.3, 38.4, 41.4 (d, J = 1.5 Hz), 59.1, 68.7, 71.8, 79.6 (d, J = 22.1 Hz), 84.7 (d, J = 27.5 Hz), 97.5, 123.5 (d, J = 266.6 Hz); ^{19}F NMR (188 MHz, CDCl_3) *syn*-isomer: δ = –113.7 (s), *anti*-isomer: δ = –110.9 (d, J = 16.9 Hz); IR (neat) 3235, 2961, 2928, 1450, 1379, 1346, 1296, 1242, 1170, 1120, 1026, 981, 855, 750 cm^{-1} ; MS m/z (rel intensity) 428 ($M^+ + 2$, 0.04), 426 (M^+ , 0.04), 208 (11), 185 (2), 146 (4), 127 (29), 115 (100). HRMS Found: m/z 426.1775. Calcd for $\text{C}_{19}\text{H}_{36}\text{BrFO}_4$: M, 426.1781.

5-Bromo-5-fluoro-6-(2-methoxyethoxy)methoxy-7-methyl-3-propyl-4-octanol (4i): This was isolated in 46% yield as a 92 : 8 diastereomeric mixture, a colorless oil, R_f 0.24 (hexane-ethyl acetate = 4 : 1). ^1H NMR (200 MHz, CDCl_3) δ = 0.93 (t, J = 7.1 Hz, 6H), 1.08 (dt, J = 1.4, 7.0 Hz, 6H), 1.26–1.49 (m, 4H), 1.66–1.93 (m, 4H), 2.27–2.43 (m, 1H), 3.03 (s, 1H), 3.38 (s, 3H), 3.52–3.58 (m, 2H), 3.69–3.88 (m, 3H), 4.85 (d, J = 6.7 Hz, 1H), 4.92 (dd, J = 1.2, 6.5 Hz, 1H); ^{13}C NMR (50 MHz, CDCl_3) δ = 14.8 (d, J = 0.76 Hz), 15.0 (d, J = 1.1 Hz), 16.8 (d, J = 3.1 Hz), 17.5 (d, J = 3.4 Hz), 18.5 (d, J = 1.5 Hz), 22.9 (d, J = 3.4 Hz), 31.2 (d, J = 1.9 Hz), 37.3, 38.5 (d, J = 0.8 Hz), 59.1, 68.7, 71.8, 79.6 (d, J = 22.5 Hz), 85.0 (d, J = 27.1 Hz), 97.6, 123.7 (d, J = 267.0 Hz); ^{19}F NMR (188 MHz, CDCl_3) *syn*-isomer: δ = –113.4 (s), *anti*-isomer: δ = –110.6 (d, J = 17.0 Hz); IR (neat) 3240, 2963, 2934, 2876, 1468, 1367, 1294, 1242, 1199, 1174, 1130, 1041, 987, 864, 746 cm^{-1} ; MS m/z (rel intensity) 388 ($M^+ + 2$, 0.1), 386 (M^+ , 0.1), 281 (0.2), 267 (1), 210 (4), 208 (4), 115 (28), 89 (100). HRMS Found: m/z 386.1453. Calcd for $\text{C}_{16}\text{H}_{32}\text{BrFO}_4$: M, 386.1468.

5-Bromo-5-fluoro-2,2-dimethyl-4-(1-naphthyl)-6,6-dipropyl-1,3-dioxane (6): 76% yield as a mixture of diastereomers, a pale yellow oil, R_f 0.72 (hexane-ethyl acetate = 1 : 1). ^1H NMR (200 MHz, CDCl_3) *syn*-isomer: δ = 0.87–1.43 (m, 6H), 1.54–1.67 (m, 6H), 1.54–2.29 (m, 8H), 6.04 (s, 1H), 7.42–7.60 (m, 3H), 7.85–7.98

(m, 4H), *anti*-isomer: δ = 6.20 (d, J = 23.8 Hz, 1H); ^{19}F NMR (188 MHz, CDCl_3) *syn*-isomer: δ = –117.5 (s), *anti*-isomer: δ = –128.1 (d, J = 23.7 Hz); IR (neat) 3053, 2960, 2874, 2733, 1944, 1724, 1626, 1599, 1512, 1468, 1398, 1360, 1288, 1200, 1090, 1020, 985, 900, 773, 731 cm^{-1} ; MS m/z (rel intensity) 424 ($M^+ + 2$, 1.0), 422 (M^+ , 1.6), 173 (3), 171 (11), 156 (100), 127 (10), 111 (2), 79 (13), 71 (56). HRMS Found: m/z 422.1248. Calcd for $\text{C}_{22}\text{H}_{28}\text{BrFO}_2$: M, 422.1257.

1-Bromo-1-fluoro-2-(2-methoxyethoxy)methoxy-2-(1-naphthyl)-1-trimethylsilylthane (7):

To a solution of **2e** (85 mg, 0.2 mmol) and trimethylchlorosilane (38 μl , 0.3 mmol) in THF (1.0 ml)–diethyl ether (0.5 ml) was added butyllithium (1.63 M hexane solution, 0.15 ml, 0.25 mmol) dropwise via syringe at –130 $^\circ\text{C}$ under argon. The reaction mixture was stirred for 20 min before quenching sat aq. NH_4Cl soln. Workup followed by purification by column chromatography gave **7** (75 mg, 89%) as a mixture of diastereomers, a pale yellow oil, R_f 0.57 (hexane-ethyl acetate = 5 : 1). ^1H NMR (200 MHz, CDCl_3) *syn*-isomer: δ = 0.10 (s, 9H), 3.29 (s, 3H), 3.30–3.60 (m, 4H), 4.64 (d, J = 6.9 Hz, 1H), 4.84 (d, J = 6.9 Hz, 1H), 7.45–7.96 (m, 7H), *anti*-isomer: δ = 0.27 (s, 9H), 3.27 (s, 3H), 4.56 (d, J = 6.6 Hz, 1H), 4.75 (d, J = 6.6 Hz, 1H); ^{19}F NMR (188 MHz, CDCl_3) *syn*-isomer: δ = –141.1, *anti*-isomer: δ = –141.7; IR (neat) 3051, 2955, 2891, 2818, 1950, 1597, 1512, 1452, 1410, 1396, 1365, 1252, 1199, 1174, 1110, 1030, 927, 887, 847, 775, 702 cm^{-1} ; MS m/z (rel intensity) 430 ($M^+ + 2$, 1), 428 (M^+ , 1), 245 (6), 244 (12), 209 (11), 170 (6), 165 (9), 153 (13), 152 (94), 140 (2), 127 (1). HRMS Found: m/z 428.0813. Calcd for $\text{C}_{19}\text{H}_{26}\text{BrFO}_3\text{Si}$: M, 428.0819.

1-Bromo-1-fluoro-2-(1-naphthyl)ethene (8):

An ethereal solution of zinc chloride (1.0 M, 0.75 ml, 0.75 mmol) was added to a flask, and the whole was pumped out *in vacuo*. To the residue was added dichloromethane (4.0 ml) and **7** (64 mg, 0.15 mmol) dissolved in dichloromethane (2.0 ml). The reaction mixture was stirred for 3 h before quenching sat aq. NH_4Cl soln. Workup followed by purification by column chromatography gave **8** (23 mg, 62% yield) as a white powder, mp 39–43 $^\circ\text{C}$. ^1H NMR (200 MHz, CDCl_3) δ = 6.65 (d, J = 30.6 Hz, 1H), 7.44–7.59 (m, 3H), 7.68–7.72 (m, 1H), 7.81–8.01 (m, 3H); ^{13}C NMR (50 MHz, CDCl_3) δ = 110.2 (d, J = 7.8 Hz), 123.7, 125.5, 126.1, 126.6, 127.1, 127.2, 128.6, 128.8, 130.8, 133.7, 134.6 (d, J = 329.8 Hz); ^{19}F NMR (188 MHz, CDCl_3) (*E*)-isomer: δ = –69.5 (d, J = 30.6 Hz), (*Z*)-isomer: δ = –65.8 (d, J = 12.9 Hz); IR (CH_2Cl_2) 3045, 1640, 1585, 1345, 1035, 1005, 835, 800, 770, 705 cm^{-1} ; MS m/z (rel intensity)

252 ($M^+ + 2$, 19), 250 (M^+ , 20), 171 (100), 85 (20). Found: C, 57.03; H, 3.21%. Calcd for $C_{12}H_8BrF$: C, 57.40; H, 3.21%.

5-Bromo-5-fluoro-6-(2-methoxyethoxy)methoxy-7-phenyl-4-propyl-4-octanol (10):

This was obtained in 35% yield as a pale yellow oil, R_f 0.21 (hexane–ethyl acetate = 3 : 1). 1H NMR (200 MHz, $CDCl_3$) δ = 0.83–0.96 (m, 6H), 1.17–1.39 (m, 4H), 1.44 (d, J = 7.2 Hz, 3H), 1.61–1.86 (m, 4H), 3.08 (s, 1H), 3.35 (s, 3H), 3.46–3.84 (m, 5H), 4.30 (dd, J = 3.2, 4.6 Hz, 1H), 4.72 (d, J = 6.5 Hz, 1H), 4.87 (dd, J = 1.6, 6.5 Hz, 1H), 7.16–7.35 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 14.8, 14.9, 16.7 (d, J = 3.1 Hz), 17.0, 17.4 (d, J = 3.8 Hz), 37.7, 38.4, 42.3 (d, J = 2.7 Hz), 59.1, 68.8, 71.8, 79.7 (d, J = 22.5 Hz), 84.4 (d, J = 26.7 Hz), 97.6, 124.1 (d, J = 267.3 Hz), 126.5, 127.7 (d, J = 1.5 Hz), 128.7, 145.9; ^{19}F NMR (188 MHz, $CDCl_3$) δ = –110.7; IR (neat) 3450, 2963, 2931, 2876, 1603, 1495, 1454, 1379, 1294, 1242, 1199, 1039, 1026, 912, 856, 762, 733, 702 cm^{-1} . Found: C, 56.17; H, 7.72%. Calcd for $C_{21}H_{34}BrFO_4$: C, 56.23; H, 7.65%.

3–5 References

- 1) a) J. T. Welch, *Tetrahedron*, **43**, 3123 (1987), b) P. Bravo, and G. Resnati, *Tetrahedron: Asymm*, **1**, 661 (1990).
- 2) a) “*Biomedical Aspects of Fluorine Chemistry*,” ed. by R. Filler, and Y. Kobayashi, Kodansha Ltd. and Elsevier Biomedical Press: Tokyo and Amsterdam (1982); b) “*Biomedical Frontiers of Fluorine Chemistry*,” ed. by I. Ojima, J. R. McCarthy, and J. T. Welch, American Chemical Society: Washington, D. C. (1996).
- 3) J. T. Welch and K. W. Seper, *Tetrahedron Lett.*, **25**, 5247 (1984).
- 4) J. T. Welch and K. W. Eswarekrishnan, *J. Chem. Soc., Chem. Commun.*, **1985**, 186.
- 5) For a diastereoselective synthesis of α -bromo- α -fluoro- β -hydroxy ester, see K. Iseki, Y. Kuroki, and T. Kobayashi, *Tetrahedron Lett.*, **38**, 7209 (1997).
- 6) R. W. Hoffmann, H. C. Stiasny, and J. Krüger, *Tetrahedron*, **52**, 7421 (1996) and references cited therein.
- 7) a) R. W. Hoffmann and M. Julius, *J. Organomet. Chem.*, **353**, C30 (1988); b) R. W. Hoffmann and M. Julius, *Liebigs Ann. Chem.*, 811 (1991).
- 8) It is reported that a (2-methoxyethoxy)methyl (MEM) group stabilizes lithiated (di)fluoro enols against elimination of lithium fluoride by chelating the lithium atom with the ethereal oxygen atoms. a) S. T. Patel, J. M. Percy, and R. D. Wilkes, *Tetrahedron*, **51**, 9201 (1995); b) S. T. Patel, J. M. Percy, and R. D. Wilkes, *Tetrahedron Lett.*, **37**, 5183 (1996).
- 9) When OR' of **2** was OAc or F, only β -elimination reaction occurred, giving rise to the corresponding 1-bromo-1-fluoroethene derivative in good yields ($E : Z = 2 : 1$).
- 10) M. Kuroboshi, Thesis of Kyoto university (1989).
- 11) Similar stereodirecting chelation by an MEM group is proposed: R. G. Salomon, N. D. Sachinvala, S. Roy, B. Basu, S. R. Raychaudhuri, D. B. Miller, and R. B. Sharma, *J. Am. Chem. Soc.*, **113**, 3085 (1991).
- 12) T. Ishihara, K. Ichihara, and H. Yamanaka, *Tetrahedron Lett.*, **36**, 8267 (1995).
- 13) Conformations involving the interaction between lithium and fluorine also may be possible, but such a model does not explain the size effect of substituent R.
- 14) The stereochemistry of **1j** was assigned by comparison of the 1H NMR chemical shift with 1,1,1-trichloro-3-phenyl-2-butanol: M. Fujita, M. Obayashi, and T. Hiyama, *Tetrahedron*, **44**, 4135 (1988). 1H NMR ($CDCl_3$) δ = 4.14 (ddd, J = 4.3, 5.9, 12.2 Hz, 1H) for *syn*-**1j** (lit. 4.23 (dd, J = 2.5, 7.0 Hz), 4.03 (m, 1H) for *anti*-**1j** (lit. 4.10 (brs, 1H)).

Chapter 4

Stereoselective Synthesis of Fluoro Olefins

Using 1,1-Dibromo-1-fluoro-2-alkanols

Stereoselective conversion of $RR'C(OH)CFBr_2$ to (*E*)-1-bromo-1,2-difluoro olefins is achieved by fluorination with Et_2NSF_3 followed by dehydrobromination with lithium 2,2,6,6-tetramethylpiperidide, whereas (*E*)-1-bromo-1-fluoro olefins were obtained with high selectivity by acetylation of $RR'C(OH)CFBr_2$ followed by reductive elimination using $EtMgBr/(i-Pr_2)NH$. (*E*)-1-Bromo-1,2-difluoro olefins underwent a cross-coupling reaction with an aryl, alkenyl, or alkynylmetal reagent to afford the corresponding fluoro olefins with retention of configuration.

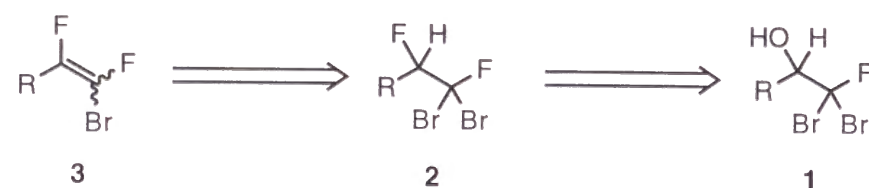
4-1 Introduction

Fluoro olefins have received growing interest recently as liquid crystalline materials,¹⁾ peptide isosteres,²⁾ and enzyme inhibitors.³⁾ Since the physical properties and biological activities heavily depend on the configuration of fluoro olefins, their stereocontrolled synthesis is desired. In the meantime, stereodefined bromo olefins are valuable precursors for the stereoselective synthesis of di-, tri-, and tetra-substituted ethenes, because many types of the cross-coupling reaction or sequential metalation-substitution reaction of bromo olefins proceed with retention of configuration.⁴⁾ Accordingly, development of an efficient and stereoselective synthesis of bromofluoro olefins⁵⁾ can lead to a new powerful method for stereodefined fluoro olefins.

4-2 Stereoselective Synthesis of Bromofluoro Olefins

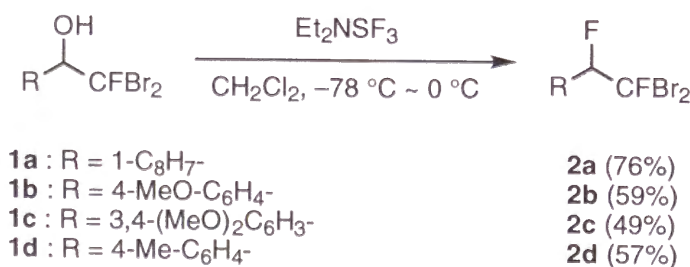
For the synthesis of 1-bromo-1,2-difluoro-1-alkenes **3**, dehydrobromination of 1,1-dibromo-1,2-difluoroalkanes **2** would be an approach of choice (Scheme 3-1). In turn, **2** can be readily prepared from **1**.

Scheme 4-1. Retrosynthesis of bromo difluoro olefin **3**.



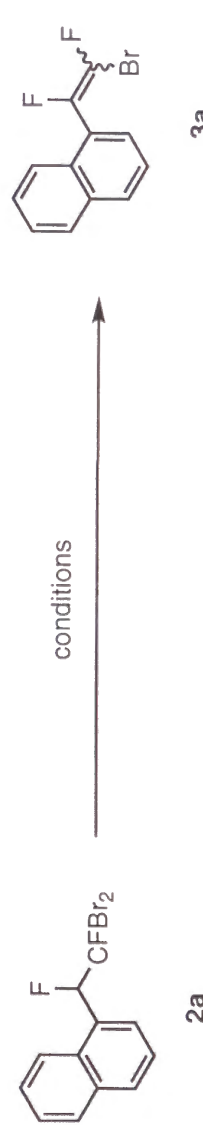
Indeed, the Author found that dibromodifluoro compounds **2** could be easily derived from **1** by fluorination with Et_2NSF_3 (1 mol amount) at $-78\text{ }^\circ\text{C}$ (Scheme 4-2).⁶⁾

Scheme 4-2. Fluorination of **1** using Et_2NSF_3 (DAST).



With **2a** as a model substrate, the Author tested various types of bases for the dehydrobromination, and summarizes the results in Table 4-1. The stereochemistry of resulting olefin **3a** was assigned on the basis of ^{19}F NMR spectroscopy: $^3J_{\text{F-F}} = 7.4\text{ Hz}$ for (*E*)-isomer and 140.6 Hz for (*Z*)-isomer. When **2a** was treated with $\text{KO}t\text{-Bu}$, $\text{KN}(\text{SiMe}_3)_2$, $\text{LiN}(\text{SiMe}_3)_2$, or $\text{LiN}(i\text{-Pr})_2$ (Table 4-1, runs 1-5), **3a** was produced in good yields but with varying selectivities. The best (*E*)-selectivity was observed with lithium 2,2,6,6-tetramethylpiperidide in THF at $-98\text{ }^\circ\text{C}$ (Table 4-1, run 6). In lieu of the metal amides or alkoxides, a base without a metal cation gave (*Z*)-**3a** preferentially. In particular, treatment of **2a** with Bu_4NOH (Table 4-1, runs 7-8) and 2-*t*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP) (Table 4-1, run 11) resulted in the formation of **3a** with 87% and 77% (*Z*)-selectivity, respectively. Thus, the stereoselectivity of the dehydrobromination was found to depend on the nature of the used base.

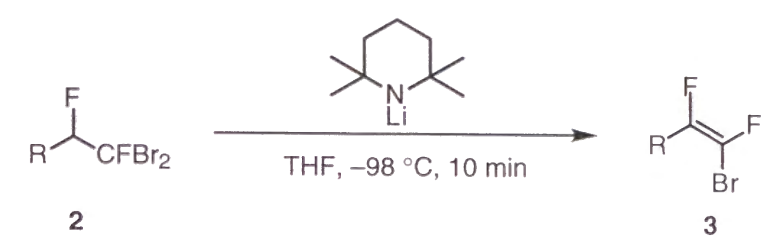
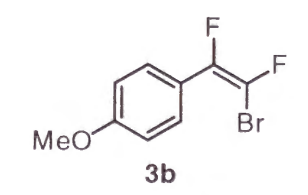
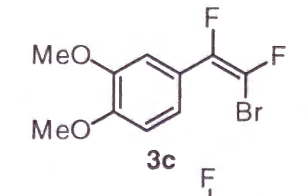
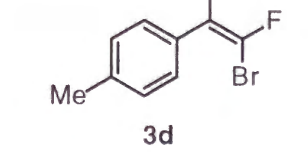
Table 4-1. Stereoselective synthesis of difluoro olefin **3a** via dehydrobromination of **2a**.

			
run	base (1.5 mol amount)	conditions	yield/% ^a
1	KO- <i>t</i> -Bu	THF, r.t., 1 h	85
2	KO- <i>t</i> -Bu	THF, -78 °C, 30 min	91
3	KN(SiMe ₃) ₂	THF/Toluene, -78 °C, 10 min	97
4	KN(SiMe ₃) ₂	THF/Et ₂ O/Toluene, -130 °C, 20 min	97
5	LiN-(<i>i</i> -Pr) ₂	THF, -98 °C, 12 min	87
6	LiN[(CMe ₂ CH ₂) ₂ CH ₂]	THF, -98 °C, 10 min	82
7	Bu ₄ NOH	CH ₂ Cl ₂ /H ₂ O, r.t., 15 min	98
8	Bu ₄ NOH	CH ₂ Cl ₂ /H ₂ O, -78 °C, 1 h	42 ^c
9	DBU	CH ₂ Cl ₂ , r.t., 1 h	95
10	DBU	CH ₂ Cl ₂ , -78 °C ~ 0 °C, 6h	84
11	BEMP	CH ₂ Cl ₂ , r.t., 12 h	93
			(<i>E</i>)- 3a : (<i>Z</i>)- 3a ^b
			48 : 52
			36 : 64
			48 : 52
			74 : 26
			85 : 15
			>99 : <1
			26 : 74
			13 : 87
			40 : 60
			40 : 60
			23 : 77

a) Isolated yield. b) *E/Z* ratio was determined by capillary gas chromatography (DB1). Stereochemistry was assigned on the basis of ¹⁹F NMR spectroscopy: ³J_{F-F} = 7.4 Hz for (*E*)-isomer and 140.6 Hz for (*Z*)-isomer. c) Substrate **2a** was recovered (40%).

The best conditions for the (*E*)-olefin synthesis using lithium 2,2,6,6-tetramethylpiperidide were applied to dibromodifluoroalkanes **2b**, **2c**, and **2d**. The results summarized in Table 4-2 demonstrate that good yields and (*E*)-selectivities were observed in all cases. The configuration of **3b**, **3c**, and **3d** was assigned on the basis of the ³J_{F-F} coupling constants: 10~11 Hz for (*E*)-isomers and 133~134 Hz for (*Z*)-isomers.⁷⁾

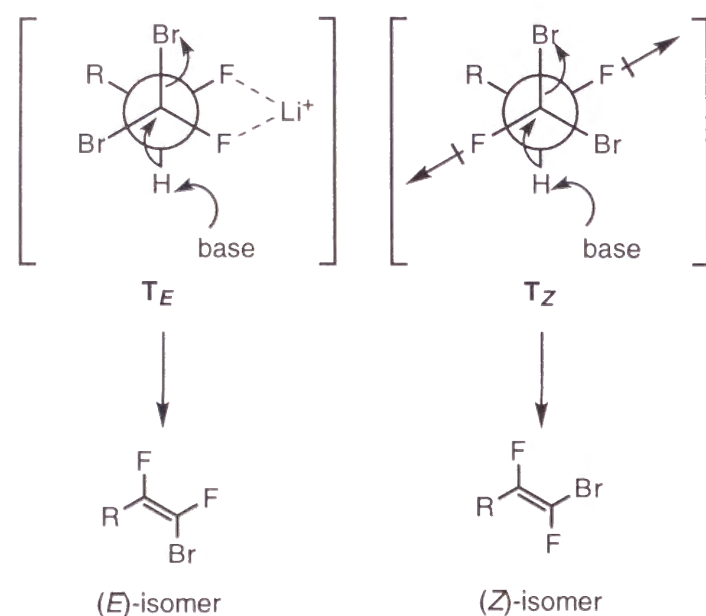
Table 4-2. Synthesis of (*E*)-2-substituted 1-bromo-1,2-difluoroethene **3**.^{a)}

			
run	product	yield/% ^{b)}	(<i>E</i>)- 3 : (<i>Z</i>)- 3 ^{c)}
1	 3b	87	92 : 8
2	 3c	90	91 : 9
3	 3d	78	91 : 9

a) The reaction was carried out in THF at -98 °C using lithium 2,2,6,6-tetramethylpiperidide (1~3 mol amount). b) Isolated yield. c) *E/Z* ratio was determined by capillary chromatography. Stereochemistry was assigned on the basis of ¹⁹F NMR spectroscopy: ³J_{F-F} = 10~11 Hz for (*E*)-isomers and 133~134 Hz for (*Z*)-isomers.

To explain the stereoselectivity of the base-dependent elimination reaction, the Author proposes transition states T_E and T_Z as depicted in Scheme 4–3. With a lithium amide base, dehydrobromination proceeded *via* T_E in which two fluorine atoms were arranged synclinal due to Li-F chelation,⁸⁾ leading to the (*E*)-isomer. On the other hand, elimination of HBr occurred with (*n*-Bu)₄NOH by way of T_Z wherein a dipole-dipole repulsion of C-F bonds played an important role, giving rise to the (*Z*)-isomer.

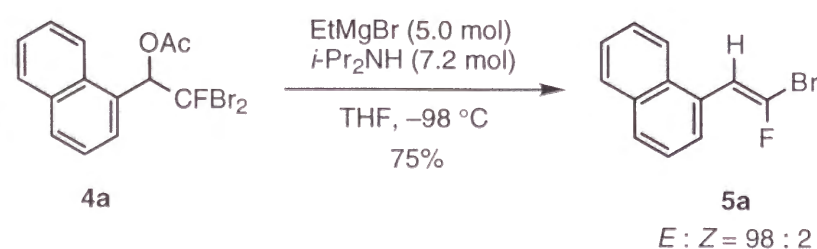
Scheme 4–3. Plausible transition states of dehydrobromination.



4–3 Stereoselective Synthesis of 1-Bromo-1-fluoroethene

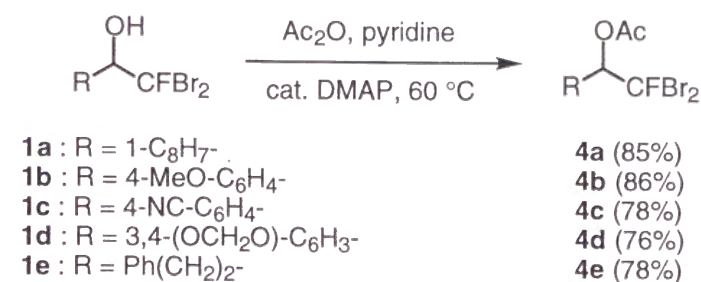
During the course of the difluoro olefin synthesis, the Author treated **4a** with a reagent prepared from EtMgBr (5 mol amount) and (*i*-Pr)₂NH (7.2 mol amount) and found that fluoro ethene **5a** was produced in 75% yield with 98% (*E*)-selectivity (Scheme 4–4).

Scheme 4–4. Synthesis of 1-bromo-1-fluoroethene **5a**.



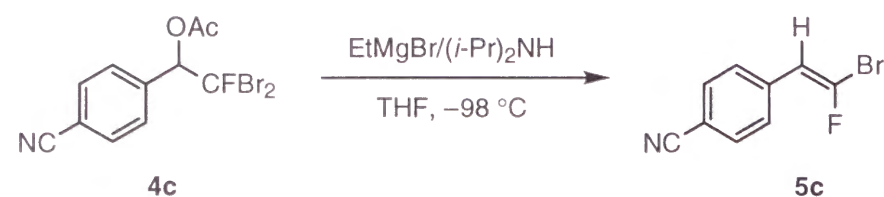
For the reductive olefination reaction, acetates **4** were found to be good substrates, as these were easily prepared by acetylation of **1** (Scheme 4–5). These results stimulated him to study the stereoselective synthesis of fluoro olefins **5** in more detail.

Scheme 4–5. Acetylation of **1**.



Using **4c** as the model substrate, the Author scrutinized the amount and mol ratio of reagents. The results summarized in Table 4–3 clearly show that the highest selectivity (*E/Z* = >99 : <1) was achieved using EtMgBr (15 molar amount) and (*i*-Pr)₂NH (5 molar amount), respectively (Table 4–3, run 1). Treatment of **4c** with EtMgBr (7.2 molar amount) and (*i*-Pr)₂NH (5 mol amount) also gave **5c** with high selectivity (95% *E*) (Table 4–3, run 2), while the reductive olefination using other equivalence of EtMgBr and (*i*-Pr)₂NH resulted in moderate selectivity (Table 4–3, runs 3–7).

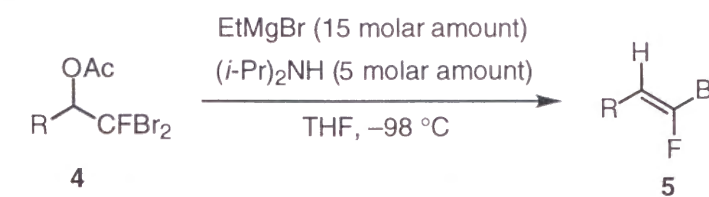
Table 4-3. Equivalence of reagents.



run	EtMgBr/ molar amount	(<i>i</i> -Pr) ₂ NH/ molar amount	yield/% ^{a)}	(<i>E</i>)- 5c : (<i>Z</i>)- 5c ^{b)}
1	15.0	5.0	89	>99 : <1
2	7.2	5.0	89	95 : 5
3	5.0	5.0	48	75 : 25
4	4.5	1.5	84	80 : 20
5	3.0	1.0	88	75 : 25
6	1.5	0.5	30	75 : 25
7	5.0	0	93	75 : 25

a) Isolated yield. b) *E/Z* ratio was determined by capillary gas chromatography. Stereochemistry was assigned on the basis of ¹H NMR and ¹⁹F NMR spectroscopy: ³J_{H-F} = 31.8 Hz for (*E*)-isomer and 14.5 Hz for (*Z*)-isomer.

The optimum reagent system was quite effective for the transformation of **4** (R = aryl; see runs 1, 2, 4, and 5) to (*E*)-**5** as summarized in Table 4-4. Diethylmagnesium in THF and 1,4-dioxane also could effect the same transformation (Table 4-4, run 3). Zinc or magnesium metal promoted the reductive elimination of **4a** and gave **5a** as well, but the stereoselectivity was lower: Zn, 50 °C, DMF, 80% yield, *E/Z* = 58 : 42; Mg, room temperature, THF, 42% yield, *E/Z* = 45 : 55.

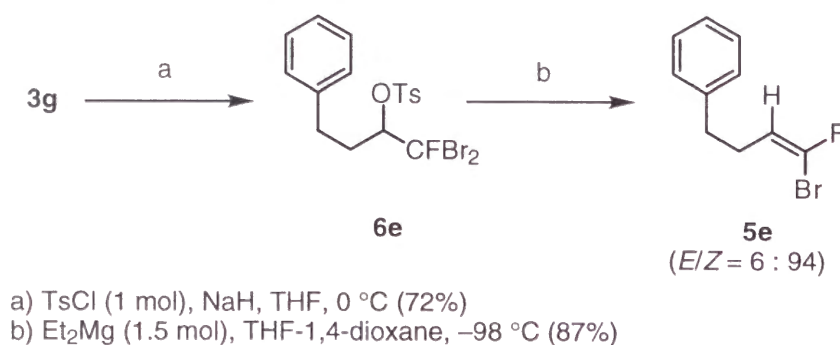
Table 4-4. Synthesis of (*E*)-2-substituted 1-bromo-1-fluoroethene **5**.

run	product	yield/% ^{a)}	(<i>E</i>)- 5 : (<i>Z</i>)- 5 ^{b)}
1		81	>99 : <1
2		84	>99 : <1
3 4 ^{c)}		89 93	>99 : <1 96 : 4
5		88	>99 : <1
6		80	33 : 67

a) Isolated yield. b) *E/Z* ratio was determined by capillary gas chromatography (DB1). Stereochemistry was assigned on the basis of ¹H NMR and ¹⁹F NMR spectroscopy: ³J_{H-F} = 30~32 Hz for (*E*)-isomer and 12~15 Hz for (*Z*)-isomer. c) The reaction was carried out in THF-1,4-dioxane at -98 °C using Et₂Mg (7.5 molar amount).

On the other hand, reduction of **4e** (R = aliphatic) gave (Z)-**5e** as the major product (Table 4-4, run 6). The *E/Z* ratio of **5e** was improved up to 6 : 94 when tosylate **6e** was reacted with Et₂Mg (1.5 molar amount) at -98 °C as illustrated in Scheme 4-6.

Scheme 4-6. Preparation of (Z)-1-bromo-1-fluoro-2-phenylethene (**5e**).



Although the real active species derived from EtMgBr and (*i*-Pr)₂NH remains yet to be explored and the reason is not clear at present why the olefinic stereochemistry resulting from the reductive elimination reverses by changing substituent R from aryl to aliphatic, the reagent system involving EtMgBr (15 molar amount) and (*i*-Pr)₂NH (5 molar amount) undoubtedly provides a method for highly stereoselective synthesis of fluoro olefins of type **5**.

4-4 Cross-Coupling Reaction of Bromofluoro Olefins

With bromo(di)fluoro olefins **3** and **5** in hand, the Author studied the carbon-carbon bond extension of **3** and **5** in order to synthesize various types of (di)fluoro olefins.¹⁹⁾ The results of the cross-coupling reaction of **3** are summarized in Table 4-5. Coupling reactions between **5** and various arylmetal reagents (metal = Si, Sn, B, or Zn) proceeded in the presence of a palladium catalyst in good to excellent yields with complete retention of the original olefin geometry (Table 4-5, runs 1-8). An alkenylborane reagent also underwent the palladium-catalyzed cross-coupling reaction of **3a** to give (Z, *E*)-**11a** in 42% yield with retention of configuration of both **3a** and the alkenylborane reagent (Table 4-5, run 9). The yield of **11a** increased to 55% when (*E*)-PhCH=CHSiMeF₂ was used as the alkenylmetal reagent with a slight loss of stereochemistry ((Z, *E*) : (*E*, *E*) = 92 : 8, run 10).¹⁰⁾ Furthermore, stereospecific coupling between **3a** and 1-alkyne occurred in the presence of PdCl₂(PPh₃)₂ together with a catalytic amount of CuI (Table 4-5, runs 11-12).

Table 4-5. Cross-coupling reaction of (*E*)-1,2-difluoroethene **3** with organometallic reagents.

run	olefin ^{a)}	R'-Mtl	Pd cat. (mol amount/10 ⁻² mol)	conditions	product ^{b)}	yield ^{c)} %
1	3a	PhSiEtF ₂	[PdCl(η ³ -C ₃ H ₅) ₂] ₂ (2.5)	TBAF, DMF, 80 °C, 64 h	7a	50
2	3a	PhSnBu ₃	PdCl ₂ (PPh ₃) ₂ (2.0)	DMF, 90 °C, 2 h	7a	88
3	3a	PhB(OH) ₂	Pd(PPh ₃) ₄ (3.0)	Na ₂ CO ₃ aq., benzene, 100 °C, 2 h	7a	99
4	3a	4-MeO-C ₆ H ₄ -ZnCl	Pd(PPh ₃) ₄ (5.0)	THF, 80 °C, 1 h	8a	80
5	3a	4-MeO-C ₆ H ₄ -B(OH) ₂	Pd(PPh ₃) ₄ (3.0)	Na ₂ CO ₃ aq., benzene, 100 °C, 2 h	8a	97
6	3a^{d)}	PhB(OH) ₂	Pd(PPh ₃) ₄ (3.0)	Na ₂ CO ₃ aq., benzene, 100 °C, 2 h	7a^{e)}	97
7	3b^{f)}	PhB(OH) ₂	Pd(PPh ₃) ₄ (3.0)	Na ₂ CO ₃ aq., benzene, 100 °C, 2 h	9d^{g)}	88
8	3c^{h)}	PhB(OH) ₂	Pd(PPh ₃) ₄ (3.0)	Na ₂ CO ₃ aq., benzene, 100 °C, 2 h	10pⁱ⁾	87
9	3a	(<i>E</i>)-PhCH=CHB(O ₂ C ₆ H ₄) ₂	Pd(PPh ₃) ₄ (3.0)	NaOEt, benzene, 80 °C, 15 h	11a^{j)}	42
10	3a	(<i>E</i>)-PhCH=CHSiMeF ₂	[PdCl(η ³ -C ₃ H ₅) ₂] ₂ (2.5)	TBAF, THF, 55 °C, 64 h	11a^{k)}	55
11	3a	PhC≡CH/CuI	PdCl ₂ (PPh ₃) ₂ (2.0)	Et ₃ N, r.t., 8 h	12a	30 ^{l)}
12	3a	HO[(CH) ₂] ₂ C≡CH/CuI	PdCl ₂ (PPh ₃) ₂ (2.0)	Et ₃ N, r.t., 16 h	13a	64 ^{m)}

a) (*E*)-Olefin (>95%) was used unless otherwise noted. b) Ratio of the *E/Z* product was >99 : <1 unless otherwise noted. c) Isolated yield. d) *E/Z* = 14 : 86. e) *E/Z* = 83 : 17. f) *E/Z* = 89 : 11. g) *E/Z* = 12 : 88. h) *E/Z* = 91 : 9. i) *E/Z* = 11 : 89. j) (*Z*, *E*)-Diene only was produced. k) (*Z*, *E*) : (*E*, *E*) = 92 : 8. l) Substrate **3a** (68%) was recovered. m) Recovery of **3a** was 30%.

4-5 Derivation of Bromofluoro Olefins via Lithiation

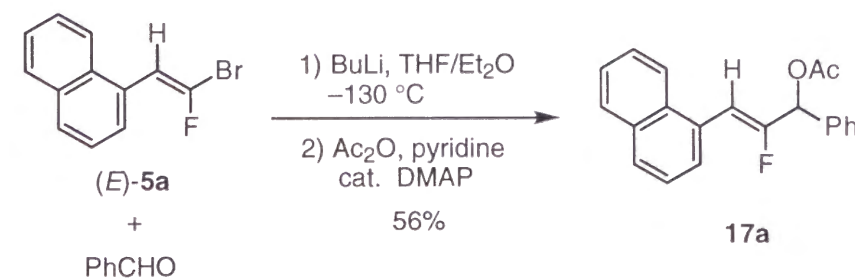
In addition to the cross-coupling approach, a two-step procedure involving a sequential metalation-substitution of bromo(di)fluoro olefins is also effective for one pot elaboration of a carbon framework.¹¹⁾ Indeed, bromine-lithium exchange of both difluoroethene (*E*)-**3a** and monofluoroethene **5a** with butyllithium at $-130\text{ }^{\circ}\text{C}$ followed by reaction with electrophiles gave the corresponding products **14a~16a** and **17a**, respectively,¹²⁾ with retention of configuration (Table 4-6 and Scheme 4-7).

Table 4-6. Lithiation of (*E*)-**3a** and the reaction with electrophiles.

run	electrophile	product	yield/% ^{a)}
1	CD ₃ OD		96
2	Me ₃ SiCl		97
3	1) PhCHO 2) Ac ₂ O		66 ^{b)}

a) Isolated yield. b) The product **16a** was isolated after acetylation.

Scheme 4-7. Lithiation of (*E*)-**5a** and reaction with benzaldehyde.



4-6 Summary

Transformation of 1,1-dibromo-1-fluoro-2-alkanols **1** obtained in Chapter 2 to difluoro olefins **7~16** is successfully achieved through fluorination, dehydrobromination, and cross-coupling reactions. Monofluoro olefins of type **17a** should be available via acetylation of **1**, stereoselective reductive elimination, and sequential lithiation-substitution. The sequence of transformations using tribromofluoromethane as a fluorine source allows us to obtain stereoselectively a wide variety of fluoro olefins that have been receiving growing interest in a broad area of medicinal, agricultural, and material sciences.

4-7 Experimental

General Procedure Fluorination of 1.

To a solution of (diethylamino)trifluorosulfur (0.92 ml, 7.0 mmol) in dichloromethane (6 ml) was added alcohol **1** (6.0 mmol) in dichloromethane (6 ml) at -78°C . The reaction mixture was allowed to warm up to 0°C over a period of 1.5 h, and was quenched with sat. NaHCO_3 aq. solution. The organic layer was separated. The aq. layer was extracted with dichloromethane (30 ml x 5). Combined organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by silica-gel column chromatography to give 1,1-dibromo-1,2-difluoroethane **2**.

1,1-Dibromo-1,2-difluoro-2-(1-naphthyl)ethane (2a): Prepared in 76% yield as a colorless oil, R_f 0.60 (hexane–dichloromethane = 7 : 1). ^1H NMR (200 MHz, CDCl_3) δ = 6.55 (dd, J = 9.9, 42.9 Hz, 1H), 7.53–7.61 (m, 3H), 7.90–8.05 (m, 4H); ^{13}C NMR (50 MHz, CDCl_3) δ = 94.1 (dd, J = 25.0, 193.0 Hz), 96.5 (dd, J = 35.7, 323.4 Hz), 123.5 (d, J = 2.63 Hz), 125.0, 126.2, 127.1, 127.8 (d, J = 8.6 Hz), 127.9 (d, J = 19.5 Hz), 129.2, 131.3, 131.6, 133.7; ^{19}F NMR (188 MHz, CDCl_3) δ = -167.4 (dd, J = 29.5, 42.9 Hz), -65.5 (dd, J = 11.1, 29.5 Hz); IR (neat) 3050, 1520, 1250, 1175, 1120, 1095, 1085, 1045, 1025, 980, 940, 820, 800, 790, 775, 725, 710 cm^{-1} ; MS m/z (rel intensity) 353 (M^+ +5, 0.8), 352 (M^+ +4, 6), 351 (M^+ +3, 1.4), 350 (M^+ +2, 12), 349 (M^+ +1, 0.8), 348 (M^+ , 6), 190 (7), 189 (19), 188 (9), 160 (20), 159 (100). Found: C, 41.40; H, 2.16%. Calcd for $\text{C}_{12}\text{H}_8\text{Br}_2\text{F}_2$: C, 41.18; H, 2.30%.

1,1-Dibromo-1,2-difluoro-2-(4-methoxyphenyl)ethane (2b): Isolated in 59% yield as a colorless oil, R_f 0.58 (hexane–dichloromethane = 2 : 1). ^1H NMR (200 MHz, CDCl_3) δ = 3.84 (s, 3H), 5.63 (dd, J = 10.7, 43.5 Hz, 1H), 6.94 (d, J = 8.2 Hz, 2H), 7.47 (d, J = 8.2 Hz, 2H); ^{13}C NMR (50 MHz, CDCl_3) δ = 55.4, 96.8 (dd, J = 34.4, 322.6 Hz), 97.2 (dd, J = 23.7, 193.4 Hz), 113.8, 123.8 (d, J = 21.6 Hz), 129.9 (dd, J = 1.2, 6.1 Hz), 161.2; ^{19}F NMR (188 MHz, CDCl_3) δ = -167.1 (dd, J = 28.2, 43.5 Hz), -67.0 (dd, J = 10.7, 28.2 Hz); IR (neat) 1605, 1580, 1510, 1460, 1300, 1290, 1250, 1180, 1120, 1090, 1065, 1025, 1000, 940, 825, 795, 735 cm^{-1} ; MS m/z (rel intensity) 332 (M^+ +4, 1), 331 (M^+ +3, 14), 330 (M^+ +2, 3), 329 (M^+ +1, 29), 328 (M^+ , 2), 327 (M^+ –1, 15), 250 (18), 248 (18), 170 (68), 139 (100). Found: C, 32.88; H, 2.46%. Calcd for $\text{C}_9\text{H}_8\text{Br}_2\text{F}_2\text{O}$: C, 32.76; H, 2.44%.

1,1-Dibromo-1,2-difluoro-2-(3,4-dimethoxyphenyl)ethane (2c): This product was obtained in 49% yield as a colorless oil, R_f 0.55 (hexane–dichloromethane = 1 : 2). ^1H NMR (200 MHz, CDCl_3) δ = 3.90 (s, 6H), 5.62 (dd, J = 10.7, 43.4 Hz, 1H), 6.94 (m, 3H); ^{13}C NMR (50 MHz, CDCl_3) δ = 56.1, 96.5 (dd, J = 34.4, 322.9

Hz), 97.2 (dd, J = 23.8, 193.8 Hz), 110.5, 111.1 (d, J = 5.6 Hz), 121.8 (d, J = 6.6 Hz), 124.0 (d, J = 21.7 Hz), 148.8, 150.7; ^{19}F NMR (188 MHz, CDCl_3) δ = -166.7 (dd, J = 28.3, 43.4 Hz), -67.0 (dd, J = 10.7, 28.3 Hz); IR (neat) 1525, 1470, 1425, 1275, 1245, 1170, 1150, 1030, 805, 715 cm^{-1} ; MS m/z (rel intensity) 363 (M^+ +5, 0.5), 362 (M^+ +4, 5), 361 (M^+ +3, 1.2), 360 (M^+ +2, 10), 359 (M^+ +1, 0.7), 358 (M^+ , 5), 169 (100). Found: C, 33.63; H, 2.91%. Calcd for $\text{C}_{10}\text{H}_{10}\text{Br}_2\text{F}_2\text{O}_2$: C, 33.36; H, 2.80%.

1,1-Dibromo-1,2-difluoro-2-(4-methylphenyl)ethane (2d): This was prepared in 57% as a colorless oil, R_f 0.61 (hexane–dichloromethane = 8 : 1). ^1H NMR (200 MHz, CDCl_3) δ = 2.40 (s, 3H), 5.66 (dd, J = 10.2, 43.6 Hz, 1H), 7.25 (d, J = 8.7 Hz, 2H), 7.45 (d, J = 8.7 Hz, 2H); ^{13}C NMR (50 MHz, CDCl_3) δ = 14.1, 21.4, 96.4 (dd, J = 33.8, 322.3 Hz), 97.3 (dd, J = 23.9, 193.8 Hz), 128.4 (d, J = 6.1 Hz), 128.9 (d, J = 20.0 Hz), 129.0; ^{19}F NMR (188 MHz, CDCl_3) δ = -168.5 (dd, J = 27.8, 43.6 Hz), -66.9 (dd, J = 10.2, 27.8 Hz); IR (neat) 2930, 1615, 1520, 1205, 1190, 1130, 1095, 1075, 1030, 1010, 945, 870, 855, 805, 735, 705 cm^{-1} ; MS m/z (rel intensity) 316 (M^+ +5, 2), 315 (M^+ +4, 18), 314 (M^+ +3, 4), 313 (M^+ +2, 37), 312 (M^+ +1, 2), 311 (M^+ , 19), 235 (16), 233 (17), 191 (6), 123 (100). HRMS Found: m/z 311.8966. Calcd for $\text{C}_9\text{H}_8\text{Br}_2\text{F}_2$: M, 311.8962.

Stereoselective Dehydrobromination of 2 with Lithium 2,2,6,6-Tetramethylpiperidide.

To a solution of 2,2,6,6-tetramethylpiperidine (5.2 ml, 31 mmol) in THF (30 ml) was added a 1.6 M hexane solution of butyllithium (15.5 ml, 25 mmol) at -78°C ; the resulting solution was stirred for 30 min at 0°C . The mixture was cooled at -98°C , and a solution of **2** (17 mmol) in THF (30 ml) was added dropwise. After 10 min, the reaction mixture was quenched with 0.1 M hydrochloric acid, and the aq. layer was extracted with diethyl ether (50 ml x 5). The combined layer organic extract was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica-gel (hexane) to give 1-bromo-1,2-difluoroethene **3** as a mixture of olefinic stereoisomers. Yields and product ratios are listed in Table 4–1 and Table 4–2.

(E)-1-Bromo-1,2-difluoro-2-(1-naphthyl)ethene (3a): This olefin was produced in 82% yield as colorless needles, mp $36\text{--}37^{\circ}\text{C}$. ^1H NMR (200 MHz, CDCl_3) δ = 7.45–7.68 (m, 4H), 7.86–8.00 (m, 3H); ^{13}C NMR (50 MHz, CDCl_3) δ = 124.8 (d, J = 1.0 Hz), 124.9 (d, J = 1.9 Hz), 125.5 (d, J = 21.0 Hz), 126.6, 127.3 (d, J = 1.0 Hz), 128.3 (dd, J = 39.4, 319.7 Hz), 130.0 (dd, J = 2.9, 2.9 Hz), 131.3 (d, J = 4.0 Hz), 131.5 (d, J = 2.8 Hz), 133.5 (d, J = 1.7 Hz), 143.3 (dd, J = 14.4, 256.4 Hz);

^{19}F NMR (188 MHz, CDCl_3) $\delta = -111.0$ (dd, $J = 1.0, 7.4$ Hz), -101.6 (d, $J = 7.4$ Hz); IR (neat) 1300, 1255, 1195, 1150, 1125, 1065, 1025, 1005, 951, 800, 780 cm^{-1} ; MS m/z (rel intensity) 270 ($\text{M}^+ + 2$, 10), 268 (M^+ , 10), 190 (12), 189 (100), 188 (72), 170 (16), 169 (15), 168 (9), 94 (19). Found: C, 53.51; H, 2.31%. Calcd for $\text{C}_{12}\text{H}_7\text{BrF}_2$: C, 53.56; H, 2.62%.

Following spectra were assigned to a minor product (**Z**)-**3a**: ^1H NMR (200 MHz, CDCl_3) $\delta = 7.41$ – 7.65 (m, 4H), 7.84 – 7.99 (m, 3H); ^{19}F NMR (188 MHz, CDCl_3) $\delta = -125.8$ (d, $J = 140.6$ Hz), -117.0 (d, $J = 140.6$ Hz).

1-Bromo-1,2-difluoro-2-(4-methoxyphenyl)ethene (3b): Obtained in 87% yield as a 92 : 8 mixture of stereoisomers. A colorless oil, R_f 0.34 (hexane–dichloromethane = 10 : 1). ^1H NMR (200 MHz, CDCl_3) $\delta = 3.84$ (s, 3H), 5.63 (dd, $J = 10.7, 43.5$ Hz, 1H), 6.94 (d, $J = 8.2$ Hz, 1H), 6.93 (d, $J = 8.5$ Hz, 2H), 7.58 (d, $J = 8.5$ Hz, 2H); ^{13}C NMR (50 MHz, CDCl_3) $\delta = 55.3, 113.9, 120.2$ (dd, $J = 0.9, 24.2$ Hz), 125.5 (dd, $J = 40.6, 315.6$ Hz), 129.5 (dd, $J = 3.3, 4.4$ Hz), 144.7 (dd, $J = 15.2, 144.7$ Hz), 160.9 (d, $J = 1.2$ Hz); ^{19}F NMR (188 MHz, CDCl_3) (*E*)-isomer: $\delta = -120.8$ (d, $J = 10.1$ Hz), -102.7 (d, $J = 10.1$ Hz), (*Z*)-isomer: $\delta = -141.5$ (d, $J = 133.4$ Hz), -119.9 (d, $J = 133.4$ Hz); IR (neat) 1605, 1575, 1510, 1460, 1440, 1305, 1290, 1255, 1180, 1165, 1140, 1115, 1060, 1025, 900, 830 cm^{-1} ; MS m/z (rel intensity) 252 ($\text{M}^+ + 4$, 1), 251 ($\text{M}^+ + 3$, 12), 250 ($\text{M}^+ + 2$, 83), 249 ($\text{M}^+ + 1$, 14), 248 (M^+ , 82), 236 (3), 235 (31), 234 (5), 233 (31), 220 (1), 219 (2), 218 (1), 217 (4), 208 (2), 207 (19), 206 (3), 205 (20), 138 (15), 137 (5), 136 (10), 107 (24), 92 (17), 79 (11). Found: C, 43.68; H, 3.09%. Calcd for $\text{C}_9\text{H}_7\text{BrF}_2\text{O}$: C, 43.40; H, 2.83%.

1-Bromo-1,2-difluoro-2-(3,4-dimethoxyphenyl)ethene (3c): The olefin was produced in 90% yield as a 91 : 9 mixture of stereoisomers. A colorless oil, R_f 0.38 (hexane–dichloromethane = 1 : 1). ^1H NMR (200 MHz, CDCl_3) $\delta = 3.89$ (s, 3H), 3.89 (s, 3H), 6.90 (m, 1H), 7.23 (m, 2H); ^{13}C NMR (50 MHz, CDCl_3) $\delta = 55.9, 56.0, 110.8, 120.3$ (d, $J = 24.1$ Hz), $121.3, 125.6$ (dd, $J = 40.6, 316.0$ Hz), 144.6 (dd, $J = 15.2, 249.8$ Hz), $148.8, 150.5$; ^{19}F NMR (188 MHz, CDCl_3) (*E*)-isomer: $\delta = -120.7$ (d, $J = 10.2$ Hz), -102.2 (d, $J = 10.2$ Hz), (*Z*)-isomer: $\delta = -141.0$ (d, $J = 133.1$ Hz), -119.1 (d, $J = 133.1$ Hz); IR (neat) 1600, 1520, 1465, 1415, 1342, 1315, 1275, 1260, 1223, 1180, 1145, 1075, 1025, 810 cm^{-1} ; MS m/z (rel intensity) 281 ($\text{M}^+ + 3$, 16), 280 ($\text{M}^+ + 2$, 84), 279 ($\text{M}^+ + 1$, 14), 278 (M^+ , 100), 235 (23), 220 (14), 156 (81), 113 (46). HRMS Found: m/z 277.9737. Calcd for $\text{C}_{15}\text{H}_{12}\text{F}_2\text{O}$: M, 277.9754.

1-Bromo-1,2-difluoro-2-(4-methylphenyl)ethene (3d): Obtained in 78% yield as a 91 : 9 mixture of isomers a colorless oil, R_f 0.56 (hexane–ethyl acetate = 200 : 1). ^1H NMR (200 MHz, CDCl_3) $\delta = 2.40$ (s, 3H), 7.20 (d, $J = 8.2$ Hz, 1H), 7.50 (d, J

$= 8.2$ Hz, 1H); ^{13}C NMR (50 MHz, CDCl_3) $\delta = 21.4, 125.2$ (d, $J = 23.5$ Hz), 126.0 (dd, $J = 40.6, 316.2$ Hz), 127.8 (dd, $J = 3.4, 4.5$ Hz), $129.2, 140.4, 144.9$ (dd, $J = 15.2, 250.0$ Hz); ^{19}F NMR (188 MHz, CDCl_3) (*E*)-isomer: $\delta = -121.7$ (d, $J = 10.5$ Hz), -101.6 (d, $J = 10.5$ Hz), (*Z*)-isomer: $\delta = -142.1$ (d, $J = 133.1$ Hz), -117.9 (d, $J = 133.1$ Hz); IR (neat) 1515, 1300, 1275, 1160, 1140, 1120, 1055, 1015, 900, 810 cm^{-1} ; MS m/z (rel intensity) 235 ($\text{M}^+ + 3$, 8), 234 ($\text{M}^+ + 2$, 75), 233 ($\text{M}^+ + 1$, 15), 232 (M^+ , 78), 231 ($\text{M}^+ - 1$, 8), 153 (26), 152 (14), 151 (47), 133 (100). HRMS Found: m/z 231.9709. Calcd for $\text{C}_9\text{H}_7\text{BrF}_2$: M, 231.9699.

Acetylation of 1

Acetic anhydride (1.9 ml, 20 mmol) and 4-(dimethylamino)pyridine (10 mg) were added to a mixture of crude alcohol **1** (10 mmol) and pyridine (3.2 ml, 40 mmol), and the resulting mixture was heated at 60 °C for 1 h. Excess pyridine and acetic anhydride were removed via azeotropic distillation by dilution with toluene and concentration *in vacuo*. Purification of the residue by silica-gel column chromatography afforded acetate **4**.

2,2-Dibromo-2-fluoro-1-(1-naphthyl)ethyl Acetate (4a): Obtained in 85% yield as a colorless oil, R_f 0.40 (hexane–dichloromethane = 3 : 2). ^1H NMR (200 MHz, CDCl_3) $\delta = 2.52$ (s, 3H), 7.26 (d, $J = 12.9$ Hz, 1H), 7.51 – 7.65 (m, 3H), 7.87 – 7.98 (m, 3H), 8.30 (d, $J = 8.5$ Hz, 1H); ^{13}C NMR (50 MHz, CDCl_3) $\delta = 20.9, 77.2$ (d, $J = 22.8$ Hz), 96.9 (d, $J = 324.4$ Hz), $123.6, 125.0, 126.0, 127.0, 127.8, 129.0, 129.3, 130.7, 131.9, 133.7, 168.7$; ^{19}F NMR (188 MHz, CDCl_3) $\delta = -62.2$ (d, $J = 12.4$ Hz); IR (neat) 1760, 1375, 1220, 1175, 1080, 1055, 1035, 928, 818, 795, 778, 725 cm^{-1} ; MS m/z (rel intensity) 393 ($\text{M}^+ + 5$, 0.6), 392 ($\text{M}^+ + 4$, 3), 391 ($\text{M}^+ + 3$, 1.2), 390 ($\text{M}^+ + 2$, 6), 389 ($\text{M}^+ + 1$, 0.6), 388 (M^+ , 3), 199 (17), 157 (100), 43 (41). Found: C, 42.94; H, 2.85%. Calcd for $\text{C}_{14}\text{H}_{11}\text{Br}_2\text{FO}_2$: C, 43.11; H, 2.84%.

2,2-Dibromo-2-fluoro-1-(4-cyanophenyl)ethyl Acetate (4c): Isolated in 78% yield as colorless plates, mp 82–83 °C. ^1H NMR (200 MHz, CDCl_3) $\delta = 2.23$ (s, 3H), 6.31 (d, $J = 12.1$ Hz, 1H), 7.60 – 7.68 (m, 4H); ^{13}C NMR (50 MHz, CDCl_3) $\delta = 20.7, 80.5$ (d, $J = 23.0$ Hz), 95.4 (d, $J = 322.1$ Hz), $113.8, 118.1, 129.9, 132.0, 137.8, 168.3$; ^{19}F NMR (188 MHz, CDCl_3) $\delta = -64.4$ (d, $J = 12.1$ Hz); IR (CH_2Cl_2) 2210, 1750, 1560, 1410, 1200, 1105, 1075, 1035, 1010, 920, 860, 830, 780 cm^{-1} ; MS m/z (rel intensity) 365 ($\text{M}^+ + 2$, 0.07), 363 (M^+ , 0.04), 174 (38), 145 (31), 102 (11), 43 (100). Found: C, 36.10; H, 2.22; N, 3.73%. Calcd for $\text{C}_{11}\text{H}_8\text{Br}_2\text{FNO}_2$: C, 36.20; H, 2.21; N, 3.84%.

2,2-Dibromo-2-fluoro-1-(4-methoxyphenyl)ethyl Acetate (4b):

Prepared in 86% yield as a pale yellow oil, R_f 0.50 (hexane–dichloromethane = 1 : 1). ^1H NMR (200 MHz, CDCl_3) δ = 2.20 (s, 3H), 3.81 (s, 3H), 6.24 (d, J = 13.0 Hz, 1H), 6.90 (d, J = 8.9 Hz, 2H), 7.46 (d, J = 8.9 Hz, 2H); ^{13}C NMR (50 MHz, CDCl_3) δ = 20.8, 55.3, 81.2 (d, J = 22.3 Hz), 97.4 (d, J = 323.1 Hz), 113.7, 124.9, 130.6, 160.7, 168.6; ^{19}F NMR (188 MHz, CDCl_3) δ = –63.5 (d, J = 13.0 Hz); IR (neat) 1755, 1610, 1515, 1465, 1375, 1310, 1290, 1255, 1210, 1180, 1120, 1030, 949, 929, 869, 834, 799, 766 cm^{-1} ; MS m/z (rel intensity) 373 (M^+ +5, 0.2), 372 (M^+ +4, 1.3), 371 (M^+ +3, 0.4), 370 (M^+ +2, 2.7), 369 (M^+ +1, 0.2), 368 (M^+ , 1.3), 230 (5), 179 (18), 137 (100), 108 (10), 43 (45). Found: C, 35.82; H, 2.75%. Calcd for $\text{C}_{11}\text{H}_{11}\text{Br}_2\text{FO}_3$: C, 35.71; H, 3.00%.

2,2-Dibromo-2-fluoro-1-(3,4-methylenedioxyphenyl)ethyl Acetate (4d): This acetate was prepared in 76% yield as a pale yellow powder, mp 82–84 °C. ^1H NMR (200 MHz, CDCl_3) δ = 2.20 (s, 3H), 5.99 (s, 2H), 6.19 (d, J = 13.0 Hz, 1H), 6.80 (d, J = 8.5 Hz, 1H), 6.99–7.03 (m, 2H); ^{13}C NMR (50 MHz, CDCl_3) δ = 20.8, 81.2 (d, J = 22.4 Hz), 97.0 (d, J = 323.1 Hz), 101.5, 108.0, 109.1, 123.8, 126.4, 147.7, 148.8, 168.5; ^{19}F NMR (188 MHz, CDCl_3) δ = –63.6 (d, J = 13.0 Hz); IR (CH_2Cl_2) 1745, 1490, 1480, 1440, 1360, 1205, 1090, 1025, 920 cm^{-1} ; MS m/z (rel intensity) 387 (M^+ +5, 0.4), 386 (M^+ +4, 3), 385 (M^+ +3, 0.8), 384 (M^+ +2, 6), 383 (M^+ +1, 0.4), 382 (M^+ , 3), 193 (12), 151 (100), 93 (11), 43 (39). Found: C, 34.33; H, 2.24%. Calcd for $\text{C}_{11}\text{H}_9\text{Br}_2\text{FO}_4$: C, 34.40; H, 2.36%.

1-(Dibromofluoromethyl)-3-phenylpropyl Acetate (4e): Obtained in 78% yield as a colorless oil, R_f 0.45 (hexane–ethyl acetate = 20 : 1). ^1H NMR (100 MHz, CDCl_3) δ = 2.05–2.40 (m, 2H), 2.15 (s, 3H), 2.51–2.78 (m, 2H), 5.43 (dt, J = 2.7, 9.3 Hz, 1H), 7.23–7.34 (m, 5H); ^{13}C NMR (50 MHz, CDCl_3) δ = 20.7, 31.5, 32.4, 79.0 (d, J = 21.9 Hz), 97.6 (d, J = 322.0 Hz), 126.5, 128.5, 128.7, 140.2, 169.5; ^{19}F NMR (94 MHz, CDCl_3) δ = –60.6 (d, J = 9.3 Hz); IR (neat) 2935, 1760, 1455, 1375, 1215, 1120, 1080, 1050, 984, 781, 747, 699 cm^{-1} ; MS (10 eV), m/z (rel intensity) 369 (M^+ +3, 5), 367 (M^+ +1, 10), 365 (M^+ –1, 5), 307 (14), 229 (40), 147 (100), 43 (12). Found: C, 39.36; H, 3.82%. Calcd for $\text{C}_{12}\text{H}_{13}\text{Br}_2\text{FO}_2$: C, 39.16; H, 3.56%.

Preparation of 1-Bromo-1-fluoroethene 5

A THF solution of EtMgBr (1.8 M, 25 ml, 45 mmol) was added to a solution of diisopropylamine (2.1 ml, 15 mmol) in THF (8 ml) at 0 °C. After 5 min, a white solid precipitated. The resulting suspension was stirred for 30 min at 0 °C. To the suspension cooled at –98 °C was added a THF (6 ml) solution of acetate **4** (3.0 mmol) dropwise via a syringe over a period of 30 min. After 10 min, a 0.1 M solution of

hydrochloric acid was added to the reaction mixture, and the aq. layer was extracted with diethyl ether (60 ml x 5). The combined organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo* to provide a crude product, which was purified by silica-gel column chromatography to give **5**.

1-Bromo-1-fluoro-2-(1-naphthyl)ethene (5a): Isolated in 81% yield as a white powder, mp 39–43 °C. ^1H NMR (200 MHz, CDCl_3) δ = 6.65 (d, J = 30.6 Hz, 1H), 7.44–7.59 (m, 3H), 7.68–7.72 (m, 1H), 7.81–8.01 (m, 3H); ^{13}C NMR (50 MHz, CDCl_3) δ = 110.2 (d, J = 7.8 Hz), 123.7, 125.5, 126.1, 126.6, 127.1, 127.2, 128.6, 128.8, 130.8, 133.7, 134.6 (d, J = 329.8 Hz); ^{19}F NMR (188 MHz, CDCl_3) (*E*)-isomer: δ = –69.5 (d, J = 30.6 Hz), (*Z*)-isomer: δ = –65.8 (d, J = 12.9 Hz); IR (CH_2Cl_2) 3045, 1640, 1585, 1345, 1035, 1005, 835, 800, 770, 705 cm^{-1} ; MS m/z (rel intensity) 252 (M^+ +2, 19), 250 (M^+ , 20), 171 (100), 85 (20). Found: C, 57.03; H, 3.21%. Calcd for $\text{C}_{12}\text{H}_8\text{BrF}$: C, 57.40; H, 3.21%.

1-Bromo-1-fluoro-2-(4-methoxyphenyl)ethene (5b): Obtained in 84% yield as colorless needles, mp 34–37 °C. ^1H NMR (200 MHz, CDCl_3) δ = 3.81 (s, 3H), 5.91 (d, J = 33.1 Hz, 1H), 6.85–6.90 (m, 2H), 7.30–7.37 (m, 2H); ^{13}C NMR (50 MHz, CDCl_3) δ = 55.3, 112.6 (d, J = 6.5 Hz), 114.1, 125.4 (d, J = 4.5 Hz), 129.4 (d, J = 7.1 Hz), 132.3 (d, J = 328.9 Hz), 159.2 (d, J = 2.9 Hz); ^{19}F NMR (188 MHz, CDCl_3) (*E*)-isomer: δ = –71.6 (d, J = 33.1 Hz), (*Z*)-isomer: δ = –68.3 (d, J = 15.3 Hz); IR (neat) 2980, 2960, 1670, 1625, 1535, 1485, 1355, 1330, 1315, 1275, 1205, 1060, 875 cm^{-1} ; MS m/z (rel intensity) 233 (M^+ +3, 10), 232 (M^+ +2, 97), 231 (M^+ +1, 8), 230 (M^+ , 100), 108 (73), 107 (37). Found: C, 47.02; H, 3.63%. Calcd for $\text{C}_9\text{H}_8\text{BrFO}$: C, 46.78; H, 3.49%.

1-Bromo-2-(4-cyanophenyl)-1-fluoroethene (5c): Produced in 89% yield as colorless needles, mp 114–117 °C. ^1H NMR (200 MHz, CDCl_3) δ = 6.03 (d, J = 31.8 Hz, 1H), 7.46–7.50 (m, 2H), 7.60–7.65 (m, 2H); ^{13}C NMR (50 MHz, CDCl_3) δ = 111.3 (d, J = 2.4 Hz), 112.0 (d, J = 6.0 Hz), 118.6, 128.5 (d, J = 7.7 Hz), 132.5, 136.81 (d, J = 334.1 Hz), 136.83 (d, J = 4.9 Hz); ^{19}F NMR (188 MHz, CDCl_3) (*E*)-isomer: δ = –63.2 (d, J = 31.8 Hz), (*Z*)-isomer: δ = –60.5 (d, J = 14.5 Hz); IR (KBr) 2926, 2855, 2224, 1925, 1734, 1684, 1649, 1605, 1558, 1541, 1504, 1412, 1329, 1307, 1277, 1205, 1178, 1124, 1066, 1043, 1014, 860, 839, 819, 808 cm^{-1} ; MS m/z (rel intensity) 257 (M^+ +2, 100), 225 (M^+ , 100), 126 (17), 99 (38). Found: C, 48.17; H, 2.07; N, 5.96%. Calcd for $\text{C}_9\text{H}_5\text{BrFN}$: C, 47.82; H, 2.22; N, 6.19%.

1-Bromo-1-fluoro-2-(3,4-methylenedioxyphenyl)ethene (5d): This was prepared in 88% yield as colorless needles, mp 52–55 °C. ^1H NMR (200 MHz, CDCl_3) δ = 5.87 (d, J = 32.6 Hz, 1H), 5.96 (s, 2H), 6.73–6.83 (m, 2H), 6.98 (d, J = 1.4 Hz,

1H); ^{13}C NMR (50 MHz, CDCl_3) δ = 101.3, 108.1 (d, J = 6.5 Hz), 108.4, 112.8 (d, J = 6.1 Hz), 122.4 (d, J = 6.0 Hz), 126.7 (d, J = 4.7 Hz), 132.6 (d, J = 329.5 Hz), 147.3 (d, J = 3.0 Hz), 148.0; ^{19}F NMR (188 MHz, CDCl_3) (*E*)-isomer: δ = -70.7 (d, J = 32.5 Hz), (*Z*)-isomer: δ = -67.8 (d, J = 15.3 Hz); IR (CH_2Cl_2) 2920, 1525, 1505, 1465, 1280, 1220, 1055, 880, 860, 850, 830 cm^{-1} ; MS m/z (rel intensity) 247 (M^+ +3, 8), 246 (M^+ +2, 80), 245 (M^+ +1, 42), 244 (M^+ , 77), 123 (7), 107 (100). HRMS Found: m/z 243.9522. Calcd for $\text{C}_9\text{H}_6\text{BrFO}_2$: M 243.9535.

1-Bromo-1-fluoro-4-phenyl-1-butene (5e): Prepared in 80% yield as a colorless oil, R_f 0.60 (hexane-dichloromethane = 20 : 1). ^1H NMR (200 MHz, CDCl_3) δ = 2.29–2.42 (m, 2H), 2.73 (t, J = 7.6 Hz, 2H), 5.52 (dt, J = 7.6, 13.0 Hz, 1H), 7.16–7.37 (m, 5H); ^{13}C NMR (50 MHz, CDCl_3) δ = 29.5 (d, J = 2.6 Hz), 34.9 (d, J = 1.9 Hz), 109.2 (d, J = 15.3 Hz), 126.4, 128.6 (d, J = 316.6 Hz), 135.8 (d, J = 314.6 Hz); ^{19}F NMR (188 MHz, CDCl_3) (*Z*)-isomer: δ = -71.9 (dt, J = 0.6, 13.0 Hz), (*E*)-isomer: δ = -75.6 (dt, J = 2.5, 31.1 Hz); IR (neat) 3040, 1680, 1505, 1470, 1130, 1010, 760, 715 cm^{-1} ; MS m/z (rel intensity) 230 (M^+ +2, 0.1), 228 (M^+ , 0.1), 149 (28), 91 (100). Found: C, 52.58; H, 4.44%. Calcd for $\text{C}_{10}\text{H}_{10}\text{BrF}$: C, 52.43; H, 4.40%.

1-(Dibromofluoromethyl)-3-phenylpropyl *p*-Toluenesulfonate (6e).

To a solution of 60% NaH (0.172 g, 4.3 mmol) in THF was added **3g** (1.41 g, 4.3 mmol) in THF (5 ml) at 0 °C. After stirring for 10 min at 0 °C, *p*-toluenesulfonyl chloride (0.82 g, 4.3 mmol) in THF (5 ml) was added at 0 °C. The resulting solution was stirred for 10 min before quenching with 0.1 M hydrochloric acid. The aq. layer was extracted with diethyl ether (20 mL x 5), and the combined extracts were dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography on silica-gel to give tosylate **6e** (1.49 g, 72% yield) as a white powder. ^1H NMR (200 MHz, CDCl_3) δ = 2.19–2.46 (m, 1H), 2.46 (m, 3H), 2.78–2.92 (m, 3H), 5.00 (ddd, J = 2.7, 6.6, 8.9 Hz, 1H), 7.19–7.40 (m, 7H), 7.81–7.88 (m, 2H); ^{13}C NMR (50 MHz, CDCl_3) δ = 21.8, 31.1, 86.0 (d, J = 20.0 Hz), 96.4 (d, J = 323.3 Hz), 126.6, 128.0, 128.6, 128.7, 129.9, 133.9, 139.9, 145.6; ^{19}F NMR (188 MHz, CDCl_3) δ = -56.7 (d, J = 6.6 Hz); IR (KBr) 1615, 1465, 1390, 1205, 1195, 1135, 1110, 1035, 945, 875, 855, 825, 780, 745, 715 cm^{-1} ; MS m/z (rel intensity) 482 (M^+ +4, 0.1), 481 (M^+ +3, 0.3), 480 (M^+ +2, 0.1), 479 (M^+ +1, 0.6), 478 (M^+ , 0.1), 477 (M^+ -1, 0.3), 229 (50), 227 (50), 147 (100), 91 (98). HRMS Found: m/z 477.9270. Calcd for $\text{C}_{17}\text{H}_{17}\text{Br}_2\text{FO}_3\text{S}$: M, 477.9250.

Cross-coupling Reaction of 1-Bromo-1,2-difluoro-ethenes.

With an organosilicon reagent: To a flame-dried test tube were added **3a** (87.5 mg, 0.3 mmol), PhSiEtF_2 (103.4 mg, 0.6 mmol), 1 M solution of TBAF in THF (0.6 ml, 0.6 mmol), $[\text{PdCl}(\eta^3\text{-C}_3\text{H}_5)]_2$ (2.8 mg, 7.5×10^{-3} mmol), and DMF (2 ml), and the resulting mixture was heated at 80 °C for 64 h. The reaction mixture was passed through a short silica-gel column to remove the catalyst, and the crude product was purified by preparative TLC to give **7a** in 50% yield.

With an organotin reagent: To a flame-dried test tube were added **3a** (87.2 mg, 0.3 mmol), tributylphenyltin (140 ml, 0.45 mmol), $\text{PdCl}_2(\text{PPh}_3)_2$ (4.2 mg, 6.0×10^{-3} mmol), and DMF (2 ml); the resulting mixture was heated at 90 °C for 2 h before quenching with aq. KF solution. The aq. layer was extracted with hexane. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. Short silica-gel column chromatography followed by preparative TLC gave **7a** in 88% yield.

With an organoboron reagent: To a flame-dried test tube were added **3a** (0.138 g, 0.51 mmol), PhB(OH)_2 (91.4 mg, 0.75 mmol), 2.0 M Na_2CO_3 aq. (0.5 ml, 1.0 mmol), $\text{Pd(PPh}_3)_4$ (17.3 mg, 0.015 mmol), and benzene (4 ml) and the resulting mixture was heated at 100 °C for 2 h. The reaction mixture was passed through a column containing anhydrous sodium sulfate and short silica-gel to remove the catalyst. The crude product was purified by preparative TLC to give **7a** in 99% yield.

(Z)-1,2-Difluoro-1-(1-naphthyl)-2-phenylethene (7a): Obtained as a colorless oil, R_f 0.54 (hexane-ethyl acetate = 20 : 1). ^1H NMR (200 MHz, CDCl_3) δ = 7.10–8.21 (m, 12H); ^{13}C NMR (50 MHz, CDCl_3) δ = 125.3 (d, J = 1.2 Hz), 125.5 (d, J = 2.3 Hz), 126.7 (d, J = 3.1 Hz), 126.8 (t, J = 2.7 Hz), 127.56 (dd, J = 1.5, 21.4 Hz), 127.56 (d, J = 1.2 Hz), 128.4 (d, J = 1.1 Hz), 128.8, 129.0 (t, J = 1.1 Hz), 129.9 (d, J = 23.7 Hz), 130.2 (dd, J = 2.7, 3.4 Hz), 131.3 (d, J = 3.1 Hz), 132.0 (dd, J = 0.76, 3.1 Hz), 133.9 (d, J = 1.9 Hz), 144.8 (dd, J = 20.8, 251.2 Hz), 147.1 (dd, J = 21.0, 246.4 Hz); ^{19}F NMR (188 MHz, CDCl_3) (*Z*)-isomer: δ = -117.6 (dd, J = 2.4, 17.5 Hz), -133.8 (d, J = 17.4 Hz), (*E*)-isomer: δ = -134.9 (d, J = 132.9 Hz), -151.5 (d, J = 132.9 Hz); IR (neat) 3061, 1578, 1508, 1495, 1446, 1398, 1277, 1248, 1186, 1128, 1091, 1072, 1057, 1020, 985, 902, 798, 777, 763 cm^{-1} ; MS m/z (rel intensity) 267 (M^+ +1, 18), 266 (M^+ , 95), 265 (M^+ -1, 41), 264 (M^+ -2, 14), 246 (100), 215 (49), 188 (29), 122 (19), 107 (29). Found: C, 81.41; H, 4.33%. Calcd for $\text{C}_{18}\text{H}_{12}\text{F}_2$: C, 81.19; H, 4.54%.

With an organozinc reagent: To a solution of 4-bromoanisole (100 ml, 0.80 mmol) in THF (2 ml) was added, 1.6 M hexane solution of butyllithium (0.50 ml, 0.80 mmol) at -78 °C. After 10 min, zinc chloride (0.80 mmol) dissolved in diethyl ether

(0.8 ml) was added at $-78\text{ }^{\circ}\text{C}$ to the solution and the resulting solution was warmed up to $0\text{ }^{\circ}\text{C}$ over a period of 2 h. The zinc reagent obtained was added via cannula to a solution of **3a** (98 mg, 0.40 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (23 mg, 0.020 mmol) in THF (2 ml). The resulting mixture was heated at $80\text{ }^{\circ}\text{C}$ for 1 h before quenching with sat. aq. NH_4Cl solution. The aq. layer was extracted with diethyl ether, and the combined organic extracts were dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by preparative TLC to afford (Z)-1,2-Difluoro-1-(4-methoxyphenyl)-2-(1-naphthyl)ethene (**8a**, 87 mg, 80%) as a white powder. ^1H NMR (200 MHz, CDCl_3) δ = 3.71 (s, 3H), 6.64 (d, J = 8.7 Hz, 2H), 7.04 (d, J = 8.7 Hz, 2H), 7.76 (m, 7H); ^{13}C NMR (50 MHz, CDCl_3) δ = 55.2, 113.7 (d, J = 0.8 Hz), 122.1 (d, J = 25.2 Hz), 125.3 (d, J = 1.1 Hz), 125.5 (d, J = 1.9 Hz), 126.7, 127.4 (d, J = 1.2 Hz), 127.7 (dd, J = 1.7, 21.5 Hz), 128.3 (dd, J = 3.4, 5.3 Hz), 128.7, 130.1 (t, J = 2.9 Hz), 131.0 (d, J = 3.1 Hz), 132.0 (d, J = 3.3 Hz), 133.9 (d, J = 1.9 Hz), 143.6 (dd, J = 21.4, 248.7 Hz), 147.0 (dd, J = 20.9, 246.1 Hz), 160.0 (d, J = 1.2 Hz); ^{19}F NMR (188 MHz, CDCl_3) δ = -120.4 (dd, J = 1.7, 18.2 Hz), -132.3 (d, J = 18.2 Hz); IR (KBr) 1689, 1605, 1576, 1514, 1466, 1417, 1302, 1279, 1250, 1180, 1128, 1082, 1062, 1032, 1020, 987, 902, 868, 839, 804, 777 cm^{-1} ; MS m/z (rel intensity) 298 ($\text{M}^+ + 2$, 0.65), 297 ($\text{M}^+ + 1$, 5), 296 (M^+ , 22), 295 ($\text{M}^+ - 1$, 4), 233 (12). HRMS Found: m/z 296.1042. Calcd for $\text{C}_{19}\text{H}_{14}\text{F}_2\text{O}$: M, 296.1013.

(Z)-1,2-Difluoro-1-(4-methoxyphenyl)-2-phenylethene (9d): In a similar way, this was prepared in 88% yield as a colorless oil. ^1H NMR (200 MHz, CDCl_3) (Z)-isomer: δ = 3.82 (s, 3H), 6.84 (m, 2H), 7.31 (m, 7H), (E)-isomer: δ = 3.87 (s, 3H); ^{19}F NMR (188 MHz, CDCl_3) (Z)-isomer: δ = -126.2 (d, J = 14.8 Hz), -131.5 (d, J = 14.9 Hz), (E)-isomer: δ = -151.3 (d, J = 120.4 Hz), -154.8 (d, J = 120.4 Hz); IR (neat) 2960, 2940, 2840, 1608, 1576, 1514, 1462, 1444, 1298, 1253, 1176, 1122, 1101, 1074, 1020, 1007, 902, 835, 765 cm^{-1} ; MS m/z (rel intensity) 248 ($\text{M}^+ + 2$, 2), 247 ($\text{M}^+ + 1$, 19), 246 (M^+ , 100), 231 (23), 215 (6), 196 (46), 123 (8), 119 (11), 89 (22), 77 (9). HRMS Found: m/z 246.0834. Calcd for $\text{C}_{15}\text{H}_{12}\text{F}_2\text{O}$: M, 246.0856.

(Z)-1,2-Difluoro-1-(3,4-dimethoxyphenyl)-2-phenylethene (10p): Obtained in 87% yield as a colorless oil. ^1H NMR (200 MHz, CDCl_3) δ = 3.67 (s, 3H), 3.87 (s, 3H), 6.76–6.80 (m, 2H), 6.93–6.97 (m, 1H), 7.26–7.48 (m, 5H); ^{19}F NMR (188 MHz, CDCl_3) (Z)-isomer: δ = -127.2 (d, J = 14.5 Hz), -130.6 (d, J = 14.5 Hz), (E)-isomer: δ = -154.0 (d, J = 120.5 Hz), -153.9 (d, J = 120.0 Hz); IR (neat) 3003, 2937, 2839, 1603, 1583, 1518, 1464, 1446, 1269, 1221, 1174, 1143, 1115, 1074, 1053, 1026, 941, 920, 860, 831, 812, 765, 733, 696 cm^{-1} ; MS m/z (rel intensity) 277 ($\text{M}^+ + 1$, 45), 276 (M^+ , 100), 260 (54), 245 (5), 202 (20), 171 (12), 170 (31), 151 (15),

137 (12), 108 (7), 100 (16), 77 (2). HRMS Found: m/z 276.0964. Calcd for $\text{C}_{16}\text{H}_{14}\text{F}_2\text{O}_2$: M 276.0962.

(1Z, 3E)-1,2-Difluoro-1-(1-naphthyl)-4-phenyl-1,3-butadiene (11a): This diene was prepared in 55% as a pale yellow oil, R_f 0.29 (hexane–ethyl acetate = 30 : 1). ^1H NMR (200 MHz, CDCl_3) δ = 6.41 (ddd, J = 1.8, 16.1, 25.1 Hz, 1H), 7.03 (d, J = 16.1 Hz, 1H), 7.20–7.29 (m, 5H), 7.50–7.66 (m, 4H), 7.92–8.13 (m, 3H); ^{13}C NMR (50 MHz, CDCl_3) δ = 115.7 (d, J = 1.9 Hz), 116.1 (d, J = 1.9 Hz), 125.2 (d, J = 1.5 Hz), 125.6 (d, J = 2.3 Hz), 126.8, 126.9 (d, J = 1.2 Hz), 127.5 (d, J = 1.5 Hz), 128.4 (d, J = 1.2 Hz), 128.7, 128.8, 129.8 (dd, J = 4.2, 12.6 Hz), 130.2 (dd, J = 2.3, 3.4 Hz), 131.5 (d, J = 2.7 Hz), 132.2 (d, J = 1.5 Hz), 133.9 (d, J = 1.9 Hz), 145.9 (dd, J = 18.7, 255.6 Hz), 146.7 (dd, J = 20.0, 248.3 Hz); ^{19}F NMR (188 MHz, CDCl_3) δ = -118.8 (d, J = 16.1 Hz), -145.4 (dd, J = 16.1, 25.1 Hz); IR (neat) 3059, 3026, 1948, 1800, 1668, 1622, 1595, 1578, 1508, 1496, 1448, 1398, 1373, 1338, 1277, 1250, 1205, 1188, 1126, 1061, 1041, 958, 933, 864, 817, 802, 777, 752, 740 cm^{-1} ; MS m/z (rel intensity) 293 ($\text{M}^+ + 1$, 22), 292 (M^+ , 100), 291 ($\text{M}^+ - 1$, 20), 272 (64), 214 (57), 201 (49), 183 (37), 128 (42). HRMS Found: m/z 292.1075. Calcd for $\text{C}_{20}\text{H}_{14}\text{F}_2$: M, 292.1064.

(Z)-1,2-Difluoro-1-(1-naphthyl)-4-phenyl-1-buten-3-yne (12a).

To a flame-dried test tube were added **3a** (0.120 g, 0.45 mmol), phenylacetylene (0.70 mmol), CuI (1.9 mg, 0.01 mmol), $\text{PdCl}_2(\text{PPh}_3)_2$ (7.0 mg, 0.01 mmol), and triethylamine (1.5 ml, 10 mmol). The resulting mixture was stirred at room temperature for 8 h before treatment with 0.1 M hydrochloric acid. The aq. layer was extracted three times with benzene. The combined organic phase was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by preparative TLC to yield **12a** (39 mg, 30% yield) as a yellow oil. R_f 0.45 (hexane–ethyl acetate = 24 : 1). ^1H NMR (200 MHz, CDCl_3) δ = 7.14–8.34 (m, 12H); ^{19}F NMR (188 MHz, CDCl_3) δ = -133.8 (d, J = 22.3 Hz), -109.9 (d, J = 22.3 Hz); IR (neat) 3061, 2210, 1672, 1578, 1510, 1489, 1442, 1398, 1334, 1296, 1252, 1192, 1180, 1159, 1128, 1064, 1049, 933, 827, 775, 754 cm^{-1} ; MS m/z (rel intensity) 291 ($\text{M}^+ + 1$, 14), 289 ($\text{M}^+ - 1$, 100), 271 (24), 252 (5), 239 (10), 144 (26), 131 (22). Found: C, 83.02; H, 4.10%. Calcd for $\text{C}_{20}\text{H}_{12}\text{F}_2$: C, 82.75; H, 4.17%.

(Z)-5,6-Difluoro-6-(1-naphthyl)-5-hexen-3-yn-1-ol (13a): This was prepared in 64% yield as a yellow oil, R_f 0.18 (hexane–dichloromethane = 1 : 3). ^1H NMR (200 MHz, CDCl_3) δ = 2.41 (ddt, J = 1.8, 4.8, 6.3 Hz, 2H), 3.42 (s, 1H), 3.47

(t, $J = 6.3$ Hz, 2H), 7.34–8.26 (m, 7H); ^{19}F NMR (188 MHz, CDCl_3) $\delta = -133.1$ (dd, $J = 4.8, 22.3$ Hz), -111.4 (d, $J = 22.3$ Hz); IR (neat) 3350, 2900, 2230, 1684, 1508, 1338, 1271, 1248, 1190, 1134, 1076, 1060, 993, 976, 931, 898, 860, 804, 775 cm^{-1} ; MS m/z (rel intensity) 258 (M^+ , 17), 238 (19), 227 (58), 207 (100), 201 (27). HRMS Found: m/z 258.0853. Calcd for $\text{C}_{16}\text{H}_{12}\text{F}_2\text{O}$: M, 258.0856.

Lithiation and Electrophilic Substitution of **3a**

To a solution of **3a** (0.27 g, 1 mmol) in THF (3 ml) and diethyl ether (1.5 ml) was added a 1.64 M hexane solution of butyllithium (0.61 ml, 1.0 mmol) at -130 °C. After stirring for 20 min at -130 °C, an electrophile (1–5 mmol) was added to the solution. The resulting solution was stirred for an additional 30 min at -130 °C and allowed to warm to -78 °C over a period of 30 min. The reaction mixture was quenched with sat. NH_4Cl aq. solution and extracted with diethyl ether (20 ml x 5). The combined organic layer was concentrated in vacuo, and the residue was purified by silica-gel column chromatography to give fluoroethene **14a** or **15a**.

(Z)-(1- ^2H)-1,2-Difluoro-2-(1-naphthyl)ethene (14a): This was isolated in 96% yield as a colorless oil, R_f 0.55 (hexane). ^1H NMR (200 MHz, CDCl_3) $\delta = 7.42$ – 7.65 (m, 4H), 7.88 – 7.97 (m, 2H), 8.13 – 8.19 (m, 1H); ^{13}C NMR (50 MHz, CDCl_3) $\delta = 125.2$ (d, $J = 3.6$ Hz), 125.8 (dd, $J = 1.4, 20.9$ Hz), 126.6 , 127.3 (d, $J = 1.1$ Hz), 128.2 (dd, $J = 2.7, 4.0$ Hz), 128.6 , 131.2 (d, $J = 1.7$ Hz), 131.7 (dd, $J = 1.4, 3.1$ Hz), 133.5 (ddt, $J = 16.6, 31.6, 258.7$ Hz), 133.7 (d, $J = 1.1$ Hz), 148.6 (ddt, $J = 3.5, 6.8, 251.9$ Hz); ^{19}F NMR (188 MHz, CDCl_3) $\delta = -158.5$ (dt, $J = 11.4, 18.4$ Hz), -125.2 (d, $J = 18.4$ Hz); IR (neat) 1700, 1525, 1320, 1270, 1210, 1170, 1125, 1075, 1010, 850, 820, 790, 780 cm^{-1} ; MS (30 eV) m/z (rel intensity) 191 (M^+ , 100), 190 (66), 189 (35), 171 (68). HRMS Found: m/z 191.0640. Calcd for $\text{C}_{12}\text{H}_7\text{DF}_2$: M, 191.0655.

(E)-1,2-Difluoro-2-(1-naphthyl)-1-trimethylsilyl ethene (15a): This olefin was prepared in 97% yield as a colorless oil, R_f 0.35 (hexane). ^1H NMR (200 MHz, CDCl_3) $\delta = -0.11$ (s, 9H), 7.43 – 7.63 (m, 4H), 7.87 – 7.99 (m, 2H), 8.06 – 8.12 (m, 1H); ^{13}C NMR (50 MHz, CDCl_3) $\delta = -2.06$ (dd, $J = 1.6, 1.6$ Hz), 124.7 (d, $J = 2.2$ Hz), 125.4 , 126.6 , 127.29 (dd, $J = 2.6, 22.8$ Hz), 127.32 (d, $J = 0.9$ Hz), 128.4 , 130.5 (dd, $J = 3.0, 3.0$ Hz), 131.5 (d, $J = 3.0$ Hz), 132.8 (d, $J = 2.9$ Hz), 133.5 (d, $J = 1.9$ Hz), 152.2 (dd, $J = 3.0, 275.2$ Hz), 154.1 (dd, $J = 14.6, 269.8$ Hz); ^{19}F NMR (188 MHz, CDCl_3) $\delta = -149.2$ (d, $J = 25.7$ Hz), -101.8 (dd, $J = 1.4, 25.7$ Hz); IR (neat) 2975, 1670, 1305, 1260, 1195, 1130, 1105, 910, 850, 810, 805, 795, 785, 765 cm^{-1} ; MS (30 eV) m/z (rel intensity) 263 (M^+ , 13), 262 ($\text{M}^+ - 1$, 62), 188 (13), 170 (100), 151 (44), 77 (54). Found: C, 68.58; H, 6.14%. Calcd for $\text{C}_{15}\text{H}_{16}\text{F}_2\text{Si}$: C, 68.67; H,

6.15%.

(Z)-2,3-Difluoro-3-(1-naphthyl)-1-phenyl-2-propenyl Acetate (16a):

A crude sample obtained from **3a** and benzaldehyde was dissolved in pyridine (0.97 ml, 12 mmol), acetic anhydride (0.57 ml, 6.0 mmol) and 4-dimethylaminopyridine (10 mg). The resulting mixture was stirred at room temperature for 3.5 h and then diluted with toluene. Concentration under reduced pressure followed by purification by silica-gel column chromatography afforded acetate **16a** (0.45 g, 66% yield). R_f 0.25 (hexane-ethyl acetate = 16 : 1). ^1H NMR (200 MHz, CDCl_3) $\delta = 2.09$ (s, 3H), 6.18 (dd, $J = 2.2, 26.2$ Hz, 1H), 7.28 – 7.35 (m, 5H), 7.56 – 7.62 (m, 4H), 7.90 – 8.03 (m, 3H); ^{13}C NMR (50 MHz, CDCl_3) $\delta = 20.8, 70.8$ (dd, $J = 2.2, 21.0$ Hz), 125.2 (d, $J = 1.0$ Hz), 125.5 (d, $J = 21.0$ Hz), $126.9, 127.1, 127.5, 128.7, 128.8, 128.9, 129.9$ (dd, $J = 2.9, 2.9$ Hz), 131.9 (d, $J = 2.9$ Hz), 132.2 (d, $J = 2.3$ Hz), 133.8 (d, $J = 2.1$ Hz), 135.8 (d, $J = 1.0$ Hz), 144.8 (dd, $J = 18.8, 259.1$ Hz), 146.3 (dd, $J = 16.3, 255.8$ Hz), 169.3 ; ^{19}F NMR (188 MHz, CDCl_3) $\delta = -148.5$ (dd, $J = 15.3, 26.2$), -117.5 (d, $J = 15.3$ Hz); IR (neat) 3051, 3034, 2974, 1795, 1720, 1605, 1579, 1508, 1496, 1464, 1454, 1398, 1367, 1342, 1290, 1257, 1186, 1143, 1122, 1082, 1061, 1035, 1020, 974, 929, 916, 866, 848, 831, 808, 792, 779, 727, 696, 659, 642, 623 cm^{-1} ; MS m/z (rel intensity) 276 (51), 229 (13), 228 (13), 127 (100), 109 (21). Found: C, 74.85; H, 4.76%. Calcd for $\text{C}_{21}\text{H}_{16}\text{F}_2\text{O}_2$: C, 74.55; H, 4.76%.

(Z)-2-Fluoro-3-(1-naphthyl)-1-phenyl-2-propenyl Acetate (17a): This was prepared in 56% as a colorless oil, R_f 0.23 (hexane-ethyl acetate = 20 : 1). ^1H NMR (200 MHz, CDCl_3) $\delta = 2.23$ (s, 3H), 6.51 (d, $J = 35.5$ Hz, 1H), 6.60 (d, $J = 14.1$ Hz, 1H), 7.30 – 7.94 (m, 12H); ^{13}C NMR (50 MHz, CDCl_3) $\delta = 21.2, 73.9$ (d, $J = 30.5$ Hz), 106.4 (d, $J = 8.3$ Hz), $124.0, 125.4, 125.8, 126.3, 127.4, 127.6, 128.3, 128.4, 128.7, 128.8, 128.9, 131.4, 133.7, 136.0, 156.9$ (d, $J = 268.4$ Hz), 169.7 ; ^{19}F NMR (188 MHz, CDCl_3) $\delta = -116.3$ (dd, $J = 14.1, 35.5$ Hz); IR (neat) 3040, 1730, 1675, 1440, 1360, 1270, 1210, 1150, 1005, 960, 775, 760, 730, 685 cm^{-1} ; MS m/z (rel intensity) 322 ($\text{M}^+ + 2$, 1), 321 ($\text{M}^+ + 1$, 4), 320 (M^+ , 25), 277 (2), 261 (10), 184 (26), 183 (100), 171 (32), 152 (12), 149 (15), 133 (35), 127 (6). HRMS Found: m/z 320.1232. Calcd for $\text{C}_{15}\text{H}_{12}\text{F}_2\text{O}$: M, 320.1213.

4-8 References

- 1) a) O. Yokokoji, T. Shimizu, and S. Kumai, JP 08040952 (1996); *Chem. Abstr.*, **124**, 316586 (1996); b) O. Yokokoji, T. Shimizu, and S. Kumai, JP 08059525 (1996); *Chem. Abstr.*, **125**, 45736 (1996); c) T. Shimizu, O. Yokokoji, and S. Kumai, JP 08119887 (1996); *Chem. Abstr.*, **125**, 128460 (1996).
- 2) T. Allmendinger, E. Felder, and E. Hungerbuehler, in "Selective Fluorination in Organic and Bioorganic Chemistry," ed. by J. T. Welch, American Chemical Society, Washington, DC (1991), p 186.
- 3) P. Bey, J. R. McCarthy, and I. A. McDolanld, in "Selective Fluorination in Organic and Bioorganic Chemistry," ed. by J. T. Welch, American Chemical Society, Washington, DC (1991), p 105.
- 4) Reviews on coupling reactions at sp^2 carbon centers: a) K. Tamao, in "Comprehensive Organic Synthesis," ed. by B. M. Trost and I. Fleming, Pergamon Press, Oxford (1991), Vol. 3, p 435; b) D. W. Knight, in "Comprehensive Organic Synthesis," ed. by B. M. Trost and I. Fleming, Pergamon Press, Oxford (1991), Vol. 3, p 481; c) K. Sonogashira, in "Comprehensive Organic Synthesis," ed. by B. M. Trost and I. Fleming, Pergamon Press, Oxford (1991), Vol. 3, p 521.
- 5) For the synthesis of bromofluoro olefins, see 1-bromo-1,2-difluoroethenes: a) R. N. Haszeldine, J. R. McAllister, and A. E. Tipping, *J. Chem. Soc., Perkin Trans. 1*, 1303 (1974); b) C. F. Smith, E. J. Soloski, and C. Tamborski, *J. Fluorine Chem.*, **4**, 35 (1974); c) R. D. Howells and H. Gilman, *J. Fluorine Chem.*, **4**, 247 (1974); d) R. D. Howells and H. Gilman, *J. Fluorine Chem.*, **5**, 99 (1975); e) N. Thoai, *J. Fluorine Chem.*, **5**, 115 (1975); f) P. Moreau, G. Dalvernny, and A. Commeyras, *J. Chem. Soc., Chem. Commun.*, **1976**, 174; g) T. Fuchikami and I. Ojima, *J. Organomet. Chem.*, **212**, 145 (1981); h) T. Gouyon, R. Sauvetre, and J. F. Normant, *J. Organomet. Chem.*, **394**, 37 (1990); i) V. A. Petrov, C. G. Krespan, and B. E. Smart, *J. Fluorine Chem.*, **77**, 139 (1996). 1-Bromo-1-fluoro ethenes: j) R. E. Banks, M. G. Barlow, W. D. Davies, R. N. Haszeldine, K. Mullen, and D. R. Taylor, *Tetrahedron Lett.*, **1968**, 3909; k) R. E. Banks, M. G. Barlow, W. D. Davies, R. N. Haszeldine, and D. R. Taylor, *J. Chem. Soc. C*, **1969**, 1104; l) R. W. Vanderhaar, D. J. Burton, and D. G. Nae, *J. Fluorine Chem.*, **1**, 381 (1972); m) R. N. Haszeldine, I.-u. -D. Mir, and A. E. Tipping, *J. Chem. Soc., Perkin Trans. 1*, **1976**, 2349; n) R. E. Banks, W. D. Davies, R. N. Haszeldine, and D. R. Taylor, *J. Fluorine Chem.*, **10**, 487 (1977); o) M. Shimizu, G.-H. Cheng, and H. Yoshioka, *J. Fluorine Chem.*, **41**, 425 (1988); p) S. Eddarir, C. Francesch, H. Mestdagh, and C. Rolando, *Tetrahedron Lett.*, **31**, 4449 (1990); q) J. Weber, L. Xu, and U. H. Brinker, *Tetrahedron Lett.*, **33**, 4537 (1992).
- 6) Fluorination of **1** (R = aliphatic) did not proceed even in refluxing CH_2Cl_2 .
- 7) M. Hudlicky, "Chemistry of Organic Fluorine Compounds (2nd edition)," Ellis Horwood, New York (1992), p 558.
- 8) Interaction of fluorine with proton or metal is discussed in: T. Yamazaki and T. Kitazume, *Tuki Gosei Kagaku Kyokai shi.*, **54**, 665 (1996).
- 9) Examples of transition metal-catalyzed cross-coupling reaction of halofluoro olefins with organometallic reagents are seen in: a) F. Tellier, R. Sauvetre, and J. F. Normant, *J. Organomet. Chem.*, **292**, 19 (1985); b) F. Tellier, R. Sauvetre, and J. F. Normant, *J. Organomet. Chem.*, **303**, 309 (1986); c) S. Eddarir, C. Francesch, H. Mestdagh, and C. Rolando, *Tetrahedron Lett.*, **31**, 4449 (1990); d) Z.-Y. Yang and D. J. Burton, *J. Fluorine Chem.*, **53**, 307 (1991).
- 10) Monitoring the reaction by capillary gas chromatography revealed that no (Z, E)-product was observed. Hence, the (Z, E)-product might be produced by isomerization of (Z, Z)-product during the workup and purification.
- 11) For the synthesis of fluoro olefins via sequential metalation-substitution of halofluoro ethenes using Li: a) J. F. Normant, *J. Organomet. Chem.*, **400**, 19 (1990); b) A. Pelter, J. Kvicala, and D. E. Parry, *J. Chem. Soc., Perkin Trans. 1*, **1995**, 2681; c) S. T. Patel, J. M. Percy, and R. D. Wilkes, *Tetrahedron Lett.*, **37**, 5183 (1996). Mg: d) P. Moreau, R. Albadri, N. Redwane, and A. Commeyras, *J. Fluorine Chem.*, **15**, 103 (1980); e) N. Redwane, P. Moreau, and A. Commeyras, *J. Fluorine Chem.*, **20**, 699 (1982); f) P. Moreau, N. Redwane, and A. Commeyras, *Bull. Soc. Chim. Fr.*, **1984**, 117. Cu: g) D. J. Burton and S. W. Hansen, *J. Am. Chem. Soc.*, **108**, 4229 (1986). Zn: h) S. W. Hansen, T. D. Spawn, and D. J. Burton, *J. Fluorine Chem.*, **35**, 415 (1987). Cd: i) D. J. Burton and S. W. Hansen, *J. Fluorine Chem.*, **31**, 461 (1986).
- 12) When benzaldehyde was used as an electrophile (Scheme 4-7), the products were isolated after acetylation since the alcohols were unstable.

Chapter 5

Preparation and Synthetic Reactions of Fluoropoly(organosilyl)methanes

Silicon-substituted fluoromethanes were prepared from tribromofluoromethane by treatment with butyllithium and chlorosilane. Bis(silyl)fluoromethane and tris(silyl)fluoromethane also were prepared using stoichiometric amounts of butyllithium and chlorosilane. Treatment of dibromo(*t*-butyldimethylsilyl)fluoromethane with butyllithium in THF at $-78\text{ }^{\circ}\text{C}$ generated bromo(*t*-butyldimethylsilyl)fluoromethylolithium, which reacted with aldehydes and ketones to give 1-fluoro-1-silyloxiranes. Alkylation of the carbenoid was also achieved efficiently. Fluoro(tributylstannyl)bis(trimethylsilyl)methane was lithiated by butyllithium to give bis(trimethylsilyl)fluoromethylolithium, which upon reaction with aldehydes produced 1-fluoroalkenyltrimethylsilanes. On the other hand, fluorotris(trimethylsilyl)methane reacted with 2 mol of aromatic aldehyde in the presence of KF/18-crown-6 to give 1,3-disubstituted 2-fluoro-2-propen-1-ol.

5-1 Introduction

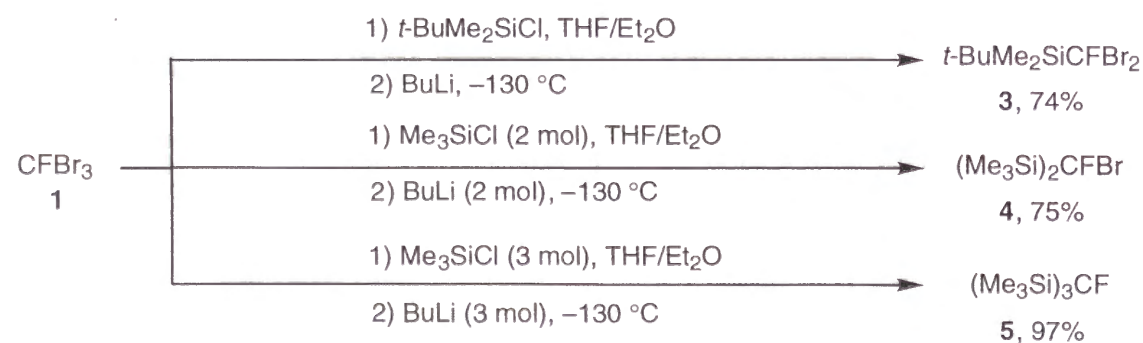
Trialkylsilyl groups not only stabilize an α -anionic center³⁾ but also serve as a clue for further transformations.⁴⁾ Accordingly, the Author focused his attention on poly(organosilyl)fluoromethanes that would be employed as new fluorine building blocks. Especially, in view of multi-functionality in bis- or tris(triorganosilyl)-methanes, these appear to be useful synthetic precursors for vinylsilanes,⁵⁾ and fluoroolefins that are attracting much attention in the field of liquid crystalline materials,⁶⁾ peptide isosteres,⁷⁾ and enzyme inhibitors.⁸⁾

5-2 Preparation of Poly(organosilyl)fluoromethanes

Dibromofluoro(trimethylsilyl)methane has been accessible via the reaction of Me_3SiCl with a reagent generated from tribromofluoromethane (**1**) and tetrakis(dimethylamino)ethylene and is a volatile and UV- and moisture-sensitive compound.⁹⁾ The Author envisaged that a *t*-butyldimethylsilyl group instead of a trimethylsilyl group would similarly stabilize the structure and facilitate the handling of the fluorosilylmethane reagent. Since the above method is not applicable to the synthesis of the bulky reagent,⁹⁾ the Author prepared silane **3** by the reaction of the corresponding carbenoid LiCFBr_2 (**2**) with *t*- BuMe_2SiCl . Thus, treatment of **1** with butyllithium in THF- Et_2O (2 : 1) at -130°C in the presence of *t*- BuMe_2SiCl gave **3** in 74% yield after purification by column chromatography on silica gel (Scheme 5-1). This in situ silylation procedure is highly effective, because **2** is labile thermally as discussed in Chapter 2.

Similarly, bromofluorobis(trimethylsilyl)methane (**4**) was prepared in 75% yield by treatment of tribromofluoromethane (1 mol) with butyllithium (2.0 mol) in the presence of Me_3SiCl (2.0 mol) in THF- Et_2O (2 : 1) at -130°C . Use of three molar amounts of butyllithium and trimethylsilyl chloride (Me_3SiCl) under the same conditions yielded fluorotris(trimethylsilyl)methane (**5**) in 97% yield (Scheme 5-1).

Scheme 5-1. Preparation of poly(organosilyl)fluoromethane.

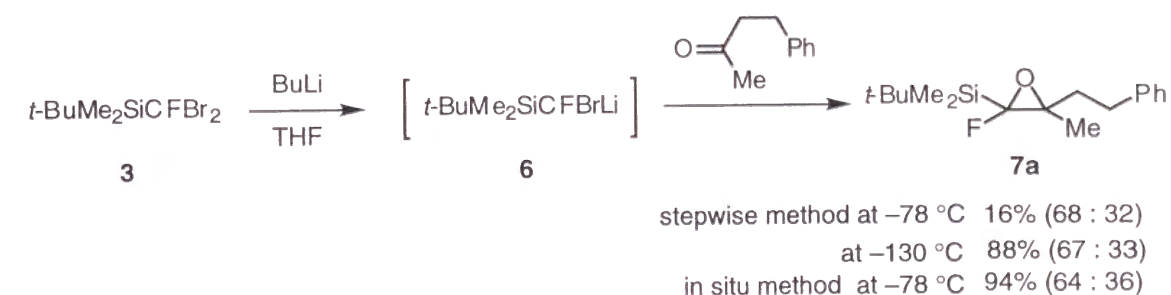


5-3-1 Generation and Carbonyl Addition of Lithium Carbenoid Derived from **3**

With **3** in hand, the Author first studied the generation and carbonyl addition using 4-phenylbutan-2-one as a carbonyl electrophile (Scheme 5-2). Treatment of **3** with butyllithium *in the presence of* 4-phenylbutan-2-one in THF at -78°C gave 1-(*t*-butyldimethylsilyl)-1,2-epoxy-1-fluoro-2-methyl-4-phenylbutane (**7a**)¹⁰⁾ in 94% yield as a 64 : 36 mixture of diastereomers.¹¹⁾

The reaction at -60°C and -42°C gave **7a** in higher yields. When 4-phenyl-2-butanone was added after the generation of **6** at -78°C , the yield of **7a** decreased drastically (16%, diastereomeric ratio = 68 : 32), whereas **7a** was obtained in 86% yield (diastereomeric ratio = 67 : 33) when the carbenoid was generated at -98°C and then allowed to react with 4-phenylbutan-2-one. Since LiCFBr_2 (**2**) must be generated at -130°C *in the presence of* an electrophile, the above results show that the silyl substituent at a fluorine-attached carbon is effective for the stabilization of fluorinated carbenoid reagents.

Scheme 5-2. Generation and carbonyl addition of **6**.



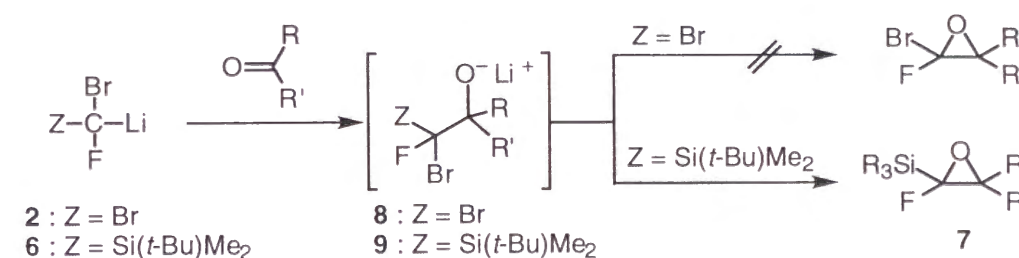
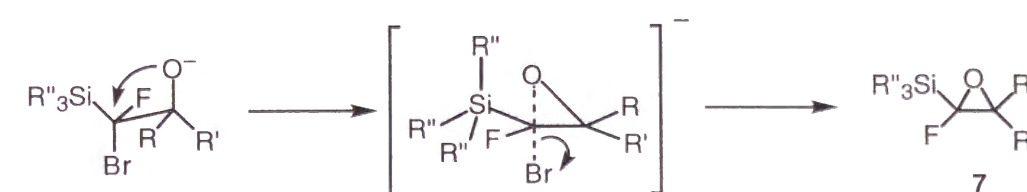
The *in-situ* procedure was applied to various aldehydes and ketones. The results are summarized in Table 5-1.

Table 5-1. Carbonyl addition of lithium carbenoid **6**.^{a)}

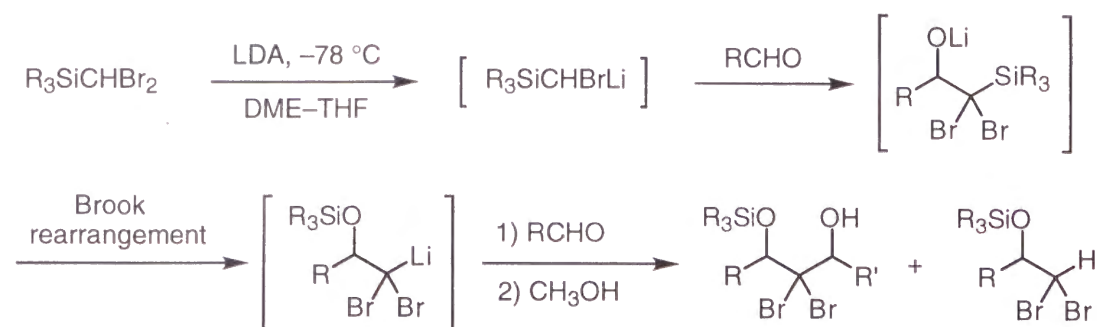
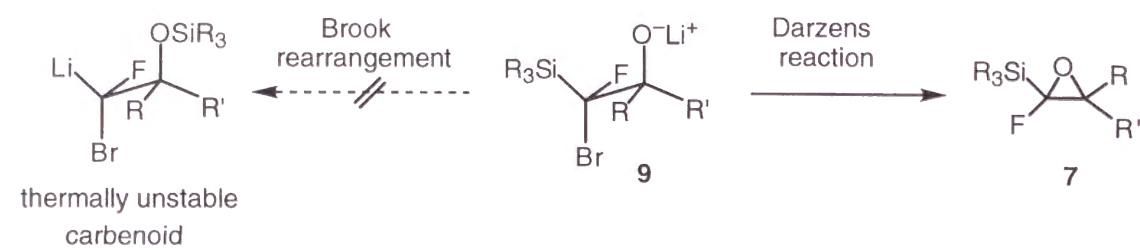
$t\text{-BuMe}_2\text{SiCFBr}_2 \quad + \quad \text{RR}'\text{C=O} \xrightarrow[\text{THF, } -78\text{ }^\circ\text{C}]{\text{BuLi}}$					
$\text{3} \qquad \qquad \qquad \text{7}$					
run	R	R'	product	yield/% ^{b)}	diastereomeric ratio ^{c)}
1	Me	Ph(CH ₂) ₂	7a	94	64 : 36
2	H	1-C ₁₀ H ₇	7b	86	94 : 6
3	H	Ph(CH ₂) ₂	7c	73	55 : 45
4	H	<i>n</i> -C ₇ H ₁₅	7d	97	56 : 44
5	-(CH ₂) ₂ CH(<i>t</i> -Bu)(CH ₂) ₂ -		7e	98	73 : 27
6	-(CH ₂) ₅ -		7f	97	—
7	Ph	Ph	7g	89	—

a) Butyllithium (1.0 mmol) was added into a solution of **3** (1.2 mmol) and a carbonyl compound (1.0 mmol) in THF (2 ml) at $-78\text{ }^\circ\text{C}$. b) Isolated yield. c) The diastereomeric ratio was determined on the basis of ¹H and ¹⁹F NMR spectroscopy. The stereochemistry was not determined.

Formation of 1-fluoro-1-silyloxiranes **7** proceeded in good to excellent yields with moderate to good diastereoselectivities and is attributed to a carbonyl addition of **6** to give alkoxide **9** followed by cyclization (Scheme 5-3). Noteworthy is that the substitution reaction took place at the fluorine-substituted carbon, a reaction considered to hardly take place intermolecularly.¹⁵⁾ Indeed, lithium alkoxide **8** derived from **2** did not cyclize even at a refluxing temperature of THF.²⁾ The ring-closure of **9** to give **7** should be attributed to the interaction of an Si-C σ* orbital with the reacting carbon *p*-orbital to stabilize the transition state of the nucleophilic substitution (Scheme 5-4).¹⁶⁾ Thus, the silicon accelerating effect for the nucleophilic substitution at the α-carbon surpasses the fluorine retarding effect.

Scheme 5-3. Effect of fluorine and silicon in the ring-closure.**Scheme 5-4.** Transition state of epoxide formation.

Oshima, Utimoto and their co-workers reported carbonyl addition of dibromosilylmethylithium, a carbenoid reagent lacking the fluorine functionality (Scheme 5-5).^{4k-o)} They observed that the corresponding lithium alkoxide underwent the Brook rearrangement rather than the Darzens type reaction (Scheme 5-6). The Author considered that the Brook rearrangement would produce a new fluorine-containing carbenoid that should be more labile than **9**. Accordingly, the Brook rearrangement should be more unfavorable.

Scheme 5-5. Brook rearrangement involved in carbenoid reaction.**Scheme 5-6.** Darzens type reaction vs Brook rearrangement.**5-3-2 Alkylation of Lithium Carbenoid 6**

As described above, addition of carbenoid reagent **6** to a carbonyl electrophile can be performed *after* the generation of the carbenoid reagent at -98°C . This observation suggests that **6** can react with an electrophile that competitively reacts with butyllithium. Thus, alkylation was carried out by the addition of an alkylating reagent after **6** was generated at -98°C . The results are shown in Table 5-2. Relatively reactive alkyl halides and sulfonates as well as chlorotrimethylsilane were applicable, and the alkylated or silylated products were isolated in good yields.¹⁷⁾

Table 5-2. Alkylation of lithium carbenoid **6**.

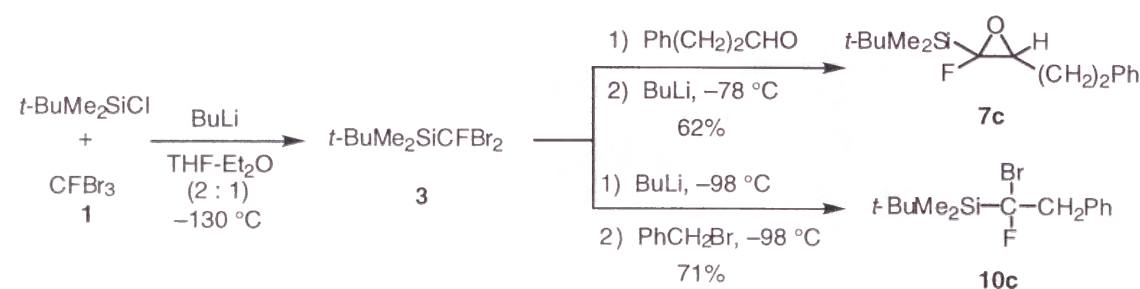
R'-X	product	yield/% ^{a)}
MeI	10a	70 ^{b)}
EtI	10b	85 ^{b)}
PhCH ₂ Br	10c	62
CH ₂ =CHCH ₂ Br	10d	69
(CH ₃) ₂ CHCH ₂ Br	10e	66
Ph(CH ₂) ₃ Br	10f	trace
Ph(CH ₂) ₃ I	10f	81
Ph(CH ₂) ₃ OTf	10f	83
CH ₂ =CH(CH ₂) ₃ OTf	10g	90
Me ₃ SiCl	10h	74

a) Isolated yield. b) Yields were determined by ¹H NMR using 1,1,2-trichloroethylene as an internal standard.

5-3-3 One-pot Synthesis of 7 and 10 from Tribromofluoromethane

Synthetic utility of carbenoid reagent **6** is demonstrated by a sequential one-pot operation involving preparation of **3**, generation of **6**, and carbonyl addition or alkylation (Scheme 5-7). Thus, **1** (1.5 mol) was treated with butyllithium (1.5 mol) in the presence of *t*-butylchlorodimethylsilane (1.5 mol) in THF-Et₂O (2 : 1) at -130 °C. To the mixture, 3-phenylpropanal and additional butyllithium were added in this order at -78 °C to afford **7c** in 62% yield. On the other hand, butyllithium (1.2 mol) and benzyl bromide (1 mol) were successively added to the solution of **3** at -98 °C, giving rise to **10c** in 71% yield.

Scheme 5-7. One-pot reaction of **7** and **10** using silicon-substituted lithium carbenoid.



Fluorine-substituted oxiranes are attractive synthetic intermediates¹²⁾ as useful building blocks for the synthesis of organofluorine compounds that are finding extensive applications in pharmaceutical and material sciences.¹³⁾ For example, hexafluoropropene oxide is utilized as a versatile precursor of hexafluoroacetone or difluorocarbene.¹⁴⁾

5-4 Reaction of 4 with Aldehydes

The Author attempted generation of a bis(trimethylsilyl)fluoromethyl anion reagent from **4**, and subsequent aldehyde addition in order to synthesize fluoroalkenylsilanes **12**, potential intermediates applicable to various kinds of synthetic transformations.¹⁸⁾ However, treatment of **4** with butyllithium in THF at -78 °C followed by addition of 3-phenylpropanal at -98 °C failed to give desired alkenylsilane.^{12g)} Thus, the Author designed a new reagent, **11**,¹⁹⁾ that involves a stannyl group in lieu of bromine. The tin reagent, fluoro(tributylstannyl)bis(trimethylsilyl)methane (**11**) was prepared by treatment of **11** with an equimolar amount of butyllithium in THF at -78 °C and subsequent by treatment with 3-phenylpropanal at -98 °C gave successfully 1-fluoro-4-phenyl-1-trimethylsilylbut-1-ene (**12g**) in 75% yield with 93% *E*-selectivity (Scheme 5-8). When the aldehyde addition was performed at -78 °C, the yield increased at the expense of the *E/Z* selectivity. The low temperature conditions were applied to other aldehydes as summarized in Table 5-3.

Scheme 5-8. Preparation and aldehyde addition of bis(trimethylsilyl)fluoromethyl-lithium.

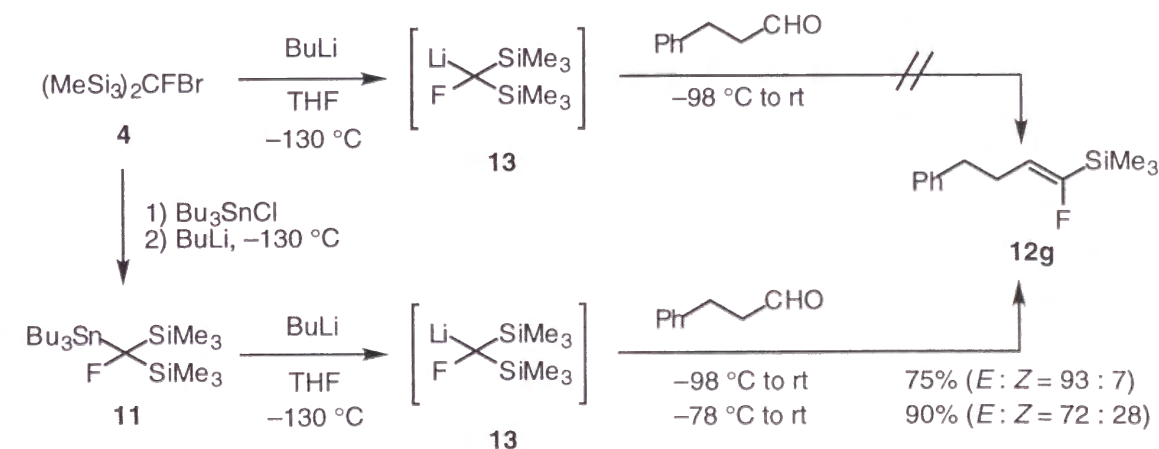


Table 5-3. Synthesis of **12** from **11**.

$ \begin{array}{c} \text{Bu}_3\text{Sn} \quad \text{SiMe}_3 \\ \diagdown \quad / \\ \text{C} \\ / \quad \diagdown \\ \text{F} \quad \text{SiMe}_3 \end{array} \xrightarrow[\text{THF, } -78^\circ\text{C}]{\text{BuLi}} \xrightarrow[-98^\circ\text{C to rt}]{\text{RCHO}} \begin{array}{c} \text{R} \quad \text{SiMe}_3 \\ \diagdown \quad / \\ \text{C} \\ / \quad \diagdown \\ \text{F} \end{array} $					
11	12				
R	product	yield/%	E	:	Z ^{a)}
Ph	12a	51	24	:	76
4-Me-C ₆ H ₄ -	12b	69	24	:	76
4-MeO-C ₆ H ₄ -	12c	98	15	:	85
4-C ₆ H ₅ -C ₆ H ₄ -	12d	87	28	:	72
(E)-PhCH=CH-	12f	86	27	:	83
Ph(CH ₂) ₂ -	12g	75	93	:	7
C ₆ F ₅ -	12h	53	>99	:	<1
4-CF ₃ -C ₆ H ₄ -	12i	98	57	:	43

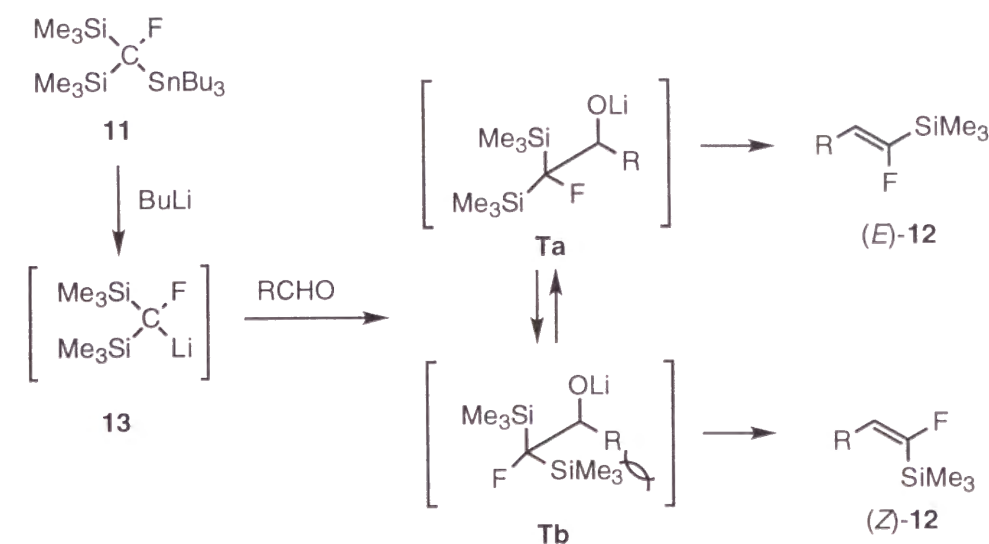
a) Stereochemistry was assigned on the basis of ¹⁹F NMR spectroscopy:

³J_{H-F} = 45.7~52.6 Hz for (E)-**12** and 33.7~38.8 Hz for (Z)-**12**.

A mechanism for the formation of 1-fluoroalkenylsilane is proposed in Scheme 5-9. Treatment of **11** with butyllithium should produce the corresponding lithium reagent by tin-lithium exchange. The lithium reagent then reacts with an aldehyde to generate lithium alkoxide which undergoes the Peterson olefination, giving rise to 1-fluoroalkenylsilane. The stereochemical outcome is tentatively explained as follows. Supposing that the Peterson olefination would occur via *syn*-elimination, two transition states in which C-OLi and C-Si bonds are displaced in an eclipsed conformation. In view of the steric repulsion between a trimethylsilyl group and R, transition state **Tb** would be disfavored. Hence, (E)-**12** would predominate. This is the case of aliphatic aldehydes and pentafluorobenzaldehyde. On the other hand, benzaldehyde and *o*-anisaldehyde gave opposite stereochemical results. The results may be explained by

electrostatic repulsion between fluorine and aromatic ring R.

Scheme 5-9. Proposed mechanism in making alkenylsilane.



5-5 Reaction of **5** with Aldehydes

The Author considered that fluorotris(trimethylsilyl)methane (**5**) should be a very useful precursor⁵⁾ of fluoro olefins as **4**.

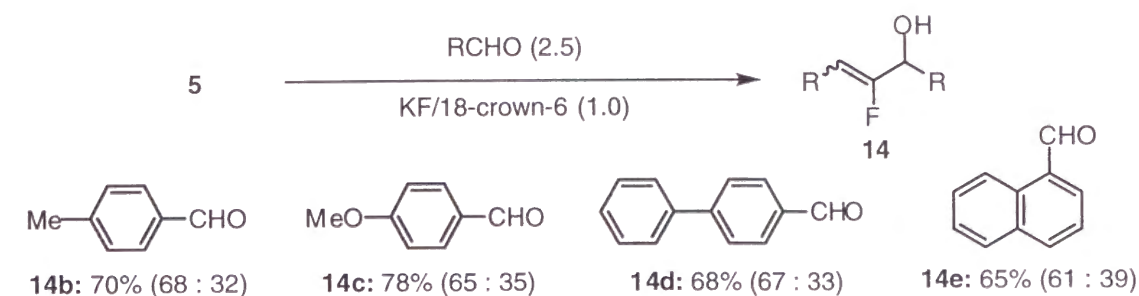
At first, he examined a fluoride ion-catalyzed reaction of **5** with benzaldehyde (Table 5-4). To a THF solution of **5** (1.0 mol) and PhCHO (1.0 mol) was added Bu₄NF (0.1 mol) at 0 °C, and the reaction mixture was allowed to warm to room temperature. Work up and purification by silica gel column chromatography gave in 35% yield 2-fluoro-1,3-diphenyl-2-propen-1-ol (**14a**, E : Z = 66 : 34), a product derived from **5** (1.0 mol) and PhCHO (2 mol) (Table 5-4, run 1). When 2.5 mol of PhCHO was used, the yield of **14a** was slightly improved (Table 5-4, run 2). The formation of the 1 : 2 adduct was much improved with a KF/18-crown-6 reagent system (Table 5-4, runs 5-6).

The conditions of run 6 could be applied to 4-MeC₆H₄CHO, 4-MeOC₆H₄CHO, 4-C₆H₅C₆H₄CHO, and 1-naphthaldehyde (Scheme 5-10), whereas cinnamaldehyde, 3-phenylpropanal, *p*-CF₃-C₆H₄CHO, *p*-CN-C₆H₄CHO, and C₆F₅CHO did not give the corresponding products. It is noteworthy that no alkenylsilane could be isolated and that the second carbonyl addition occurred smoothly in contrast to the fact that, in the presence of a fluoride catalyst, (Me₃Si)₃CH reacts with an aldehyde, as reported, to give vinylsilanes RCH=CH(SiMe₃).⁵ⁱ⁾

Table 5-4. Fluoride ion-catalyzed reaction of **5** with benzaldehyde.

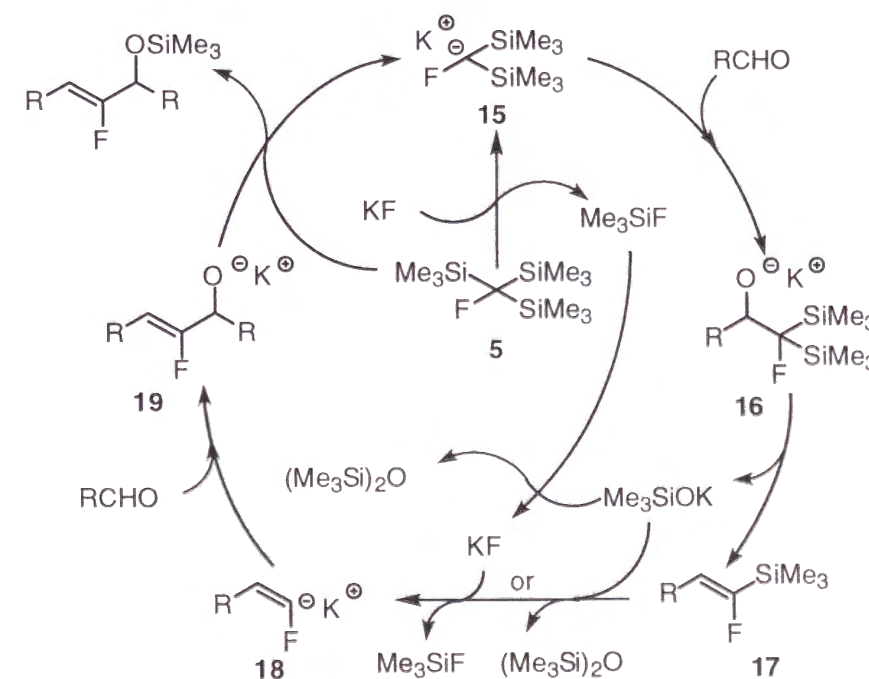
		$(\text{Me}_3\text{Si})_3\text{CF}$		$\xrightarrow[\text{F}^-]{\text{PhCHO}}$				14a	
run	PhCHO (mol)	F ⁻ (mol)	solvent	temp.	yield/%	E	:	Z	a)
1	1.0	Bu ₄ NF (0.1)	THF	0 °C to rt	35	66	:	34	
2	2.5	Bu ₄ NF (0.1)	THF	0 °C to rt	46	67	:	33	
3	2.5	Bu ₄ NF (0.5)	THF	0 °C to rt	12	63	:	37	
4	2.5	KF/18-Cr-6 (0.1)	DMF	rt	26	56	:	44	
5	2.5	KF/18-Cr-6 (0.5)	DMF	rt	72	66	:	34	
6	2.5	KF/18-Cr-6 (1.0)	DMF	rt	74	65	:	35	

a) Stereochemistry was assigned on the basis of ¹⁹F NMR spectroscopy: ³J_{H-F} = 20.4 Hz for (E)-**13a** and 39.3 Hz for (Z)-**13a**.

Scheme 5-10. Synthesis of **13** from aldehydes.

A mechanism for the formation of **14** is proposed in Scheme 5-11. First, KF activates **5** to generate fluoromethyl anion reagent **15** which reacts with an aldehyde, giving rise to potassium alkoxide **16**. The alkoxide undergoes the Peterson elimination to afford alkenylsilane **17** and Me₃SiOK which would react with Me₃SiF to produce KF and Me₃SiOSiMe₃. Alkenylsilane **17** is activated by the reproduced KF to generate alkenylpotassium reagent **18**, which reacts with another aldehyde to give adduct **19**. Alternatively, **17** might be activated by Me₃SiOK or alkoxide **19**. Finally, silicon-potassium exchange between adduct **19** and starting silane **5** affords a silyl ether of **14** and generates anion **15** again.

Scheme 5-11. Proposed mechanism.



5-6 Summary

Poly(organosilyl)fluoromethanes were easily prepared using controlled amounts of chlorosilane and butyllithium. The Author has demonstrated that 1-fluoro-1-silyloxiranes are synthesized in good yields by the reaction of a fluorine- and silyl-substituted lithium carbenoid reagents with carbonyl compounds. In addition, alkylation of the fluorinated carbenoid with alkyl halides or triflates affords the corresponding products in yields of synthetic meaning. The Author has shown that $(\text{Me}_3\text{Si})_3\text{CF}$ and $(\text{Me}_3\text{Si})_2(\text{SnBu}_3)\text{CF}$ also can be conveniently prepared and transformed into fluoro olefins by a proper activation and aldehyde addition. The products constitute a fluorine functionality important in bioactive molecules.

The present reagents provide us with convenient tools for the synthesis of monofluoro compounds.

5-7 Experimental

Dibromo(*t*-butyldimethylsilyl)fluoromethane (3)

To a solution of tribromofluoromethane (**1**) (98 μl , 1.0 mmol) and *t*-BuMe₂SiCl (0.150 g, 1.00 mmol) in THF (2 ml)–Et₂O (1 ml) was added a 1.60 M hexane solution of butyllithium (0.63 ml, 1.01 mmol) at $-130\text{ }^\circ\text{C}$ via a syringe over a period of 10 min. The resulting mixture was stirred for 0.5 h at $-130\text{ }^\circ\text{C}$ before quenching with a sat. NH₄Cl aq. solution. The aq. layer was extracted with diethyl ether (20 ml x 3). The combined extracts were dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by silica-gel column chromatography to afford **3** (0.23 g, 74% yield) as a colorless oil, R_f 0.66 (hexane). ¹H NMR (200 MHz, CDCl₃) δ = 0.32 (s, 6H), 1.09 (s, 9H); ¹³C NMR (50 MHz, CDCl₃) δ = -6.6 (d, J = 1.1 Hz), 18.5, 27.4 (d, J = 1.1 Hz), 103.9 (d, J = 339.2 Hz); ¹⁹F NMR (188 MHz, CDCl₃) δ = -70.7 ; IR (neat) 2967, 2934, 2863, 2361, 1472, 1464, 1397, 1368, 1256, 1032, 936, 841, 779, 745, 698, 662 cm⁻¹. Found: C, 27.20; H, 4.90%. Calcd for C₇H₁₅Br₂FSi: C, 27.47; H, 4.94%.

Bromobis(trimethylsilyl)fluoromethane (4)

To a solution of tribromofluoromethane (0.98 ml, 10 mmol) and Me₃SiCl (2.67 ml, 21 mmol) in THF (20 ml)–Et₂O (10 ml) was added a 1.59 M hexane solution of butyllithium (12.6 ml, 20 mmol) dropwise at $-130\text{ }^\circ\text{C}$ under an argon atmosphere. The resulting mixture was stirred for 30 min at $-130\text{ }^\circ\text{C}$, gradually warmed to room temperature, and stirred for 12 h before quenching with sat. aq. NH₄Cl solution (30 ml). The organic layer was separated; the aqueous layer was extracted with Et₂O (50 ml x 3). The combined organic layer was dried over anhydrous MgSO₄, filtered and concentrated *in vacuo*. The residue was purified by vacuum distillation to afford **4** (1.94 g, 75% yield) as a colorless oil. Bp $100\text{ }^\circ\text{C}/20\text{ mmHg}$. ¹H NMR (200 MHz, CDCl₃) δ = 0.23 (s, 18H); ¹³C NMR (50 MHz, CDCl₃) δ = -2.4 (d, J = 1.9 Hz), 113.0 (d, J = 260.6 Hz); ¹⁹F NMR (188 MHz, CDCl₃) δ = -173.4 ; IR (neat) 2961, 1905, 1410, 1254, 953, 901, 849, 812, 764, 704, 619 cm⁻¹; MS m/z (rel intensity) 259 (M^+ +3, 0.06), 258 (M^+ +2, 0.36), 257 (M^+ +1, 0.07), 256 (M^+ , 0.33) 73 (100). HRMS Found: m/z 256.0111. Calcd for C₇H₁₈BrFSi₂: M, 256.0114.

Fluorotris(trimethylsilyl)methane (5)

To a solution of tribromofluoromethane (0.98 ml, 10 mmol) and Me₃SiCl (4.20 ml, 33 mmol) in THF (20 ml)–Et₂O (10 ml) was added a 1.36 M hexane solution of

butyllithium (23.5 ml, 32 mmol) at $-130\text{ }^{\circ}\text{C}$ via syringe over a period of 10 min. The resulting mixture was stirred for 30 min at $-130\text{ }^{\circ}\text{C}$ before quenching with sat. aq. NH_4Cl solution (30 ml). The aqueous layer was extracted with Et_2O (50 ml x 3). The combined organic layer was dried over anhydrous MgSO_4 and concentrated *in vacuo*. The residue was purified by distillation under reduced pressure to afford **5** (2.43 g, 97% yield) as a colorless oil, bp $80\text{ }^{\circ}\text{C}/3\text{ mmHg}$. ^1H NMR (200 MHz, CDCl_3) δ = 0.16 (s, 27H); ^{13}C NMR (50 MHz, CDCl_3) δ = 0.04 (d, J = 4.6 Hz), 96.0 (d, J = 119.6 Hz); ^{19}F NMR (188 MHz, CDCl_3) δ = -263.7 ; IR (neat) 2957, 2905, 1402, 1254, 1264, 870, 849, 810, 764, 681, 615 cm^{-1} ; MS m/z (rel intensity) 252 ($\text{M}^+ + 2$, 0.1), 251 ($\text{M}^+ + 1$, 0.1), 250 (M^+ , 0.6), 235 (20), 143 (100). HRMS Found: m/z 250.1404. Calcd for $\text{C}_{10}\text{H}_{27}\text{FSi}_3$: M, 250.1405.

Generation and Carbonyl Addition of **6**

To a THF (2 ml) solution of **3** (184 mg, 0.60 mmol) and an aldehyde or ketone (0.50 mmol) was added a 1.60 M hexane solution of butyllithium (0.31 ml, 0.50 mmol) at $-78\text{ }^{\circ}\text{C}$. The resulting solution was stirred for 0.5 h at $-78\text{ }^{\circ}\text{C}$ and allowed to warm up to room temperature. The reaction mixture was quenched with a sat. NH_4Cl aq. solution and extracted with diethyl ether (20 ml x 5); the combined organic layer was dried over anhydrous sodium sulfate. Concentration *in vacuo* gave a crude compound, which was purified by silica-gel column chromatography to give oxirane **7**.

1-*t*-Butyldimethylsilyl-1,2-epoxy-1-fluoro-2-methyl-4-phenylbutane (7a): Obtained in 86% yield as a 64 : 36 mixture of isomers. A colorless oil, R_f 0.75 (hexane–ethyl acetate = 5 : 1). ^1H NMR (200 MHz, CDCl_3) major isomer: δ = 0.00–0.22 (m, 6H), 1.01 (s, 3H), 1.29 (d, J = 2.2 Hz, 9H), 1.60–2.19 (m, 2H), 2.77 (d, J = 7.4 Hz, 2H), 7.07–7.35 (m, 5H); minor isomer: (assignable peak) δ = 1.46 (s, 3H); ^{13}C NMR (50 MHz, CDCl_3) major isomer: δ = -6.8 (d, J = 2.7 Hz), -5.8 (d, J = 4.9 Hz), 16.5 (d, J = 1.1 Hz), 19.2 (d, J = 3.3 Hz), 26.6 (d, J = 1.9 Hz), 31.3 (d, J = 0.8 Hz), 35.2 (d, J = 0.8 Hz), 62.7 (d, J = 16.3 Hz), 100.6 (d, J = 290.0 Hz), 125.9, 128.3, 128.3, 141.4; minor isomer: δ = -6.6 (d, J = 3.0 Hz), -5.8 (d, J = 4.2 Hz), 16.6 (d, J = 1.1 Hz), 16.8, 26.7 (d, J = 2.3 Hz), 30.7 (d, J = 1.5 Hz), 36.7 (d, J = 3.4 Hz), 63.1 (d, J = 16.7 Hz), 100.6 (d, J = 290.3 Hz), 126.0, 128.1, 128.5, 141.3; ^{19}F NMR (188 MHz, CDCl_3) major isomer: δ = -136.5 ; minor isomer: δ = -139.1 ; IR (neat) 3029, 2955, 2932, 2860, 2361, 1605, 1497, 1474, 1464, 1381, 1364, 1252, 1050, 899, 841, 823, 808, 779, 749, 700, 683 cm^{-1} . Found: C, 69.63; H, 9.05%. Calcd for $\text{C}_{17}\text{H}_{27}\text{FOSi}$: C, 69.34; H, 9.24%.

1-*t*-Butyldimethylsilyl-1,2-epoxy-1-fluoro-2-(1-naphthyl)ethane (7b):

This epoxide was isolated in 86% yield as a 94 : 6 mixture of stereoisomers. A colorless oil, R_f 0.67 (hexane–ethyl acetate = 4 : 1). ^1H NMR (200 MHz, CDCl_3) major isomer: δ = -0.53 (s, 3H), -0.22 (s, 3H), 0.93 (s, 9H), 4.51 (s, 1H), 7.30–8.15 (m, 7H); minor isomer: (assignable peaks) δ = 0.27 (s, 3H), 0.28 (s, 3H), 4.26 (s, 1H); ^{13}C NMR (50 MHz, CDCl_3) major isomer: δ = -7.3 (d, J = 5.0 Hz), -6.8 (d, J = 2.3 Hz), 16.8 (d, J = 1.5 Hz), 26.5 (d, J = 1.1 Hz), 97.5 (d, J = 294.7 Hz), 123.2, 123.7 (d, J = 2.7 Hz), 125.1, 126.1, 126.5, 128.3, 128.7, 130.1 (d, J = 1.9 Hz), 130.8, 133.0; ^{19}F NMR (188 MHz, CDCl_3) major isomer: δ = -129.0 ; minor isomer: δ = -153.1 ; IR (neat) 3060, 2960, 2930, 2880, 2860, 1600, 1510, 1470, 1460, 1360, 1250, 1130, 975, 935, 885, 840, 800, 780, 680 cm^{-1} . Found: C, 71.60; H, 7.80%. Calcd for $\text{C}_{18}\text{H}_{23}\text{FOSi}$: C, 71.48; H, 7.66%.

1-*t*-Butyldimethylsilyl-1,2-epoxy-1-fluoro-4-phenylbutane (7c): This was produced in 73% yield as a 55 : 45 mixture of isomers. A colorless oil, R_f 0.69 (hexane–ethyl acetate = 10 : 1). ^1H NMR (200 MHz, CDCl_3) major isomer: δ = 0.03 (d, J = 0.4 Hz, 3H), 0.10 (s, 3H), 1.01 (d, J = 0.6 Hz, 9H), 1.58–2.23 (m, 2H), 2.64 (td, J = 5.9, 0.8 Hz, 1H), 2.70–2.96 (m, 2H), 7.15–7.38 (m, 5H); minor isomer: (assignable peaks) δ = 0.14 (d, J = 0.5 Hz, 3H), 0.20 (s, 3H), 3.05 (ddd, J = 1.9, 4.5, 8.2 Hz, 1H); ^{13}C NMR (50 MHz, CDCl_3) major isomer: δ = -8.7 (d, J = 3.0 Hz), -8.2 (d, J = 3.0 Hz), 16.5 (d, J = 0.8 Hz), 26.5 (d, J = 1.5 Hz), 28.4 (d, J = 2.3 Hz), 32.3, 58.2 (d, J = 145.2 Hz), 96.4 (d, J = 295.3 Hz), 126.1, 128.3, 128.4, 141.0; minor isomer: δ = -7.0 (d, J = 3.0 Hz), -6.3 (d, J = 4.2 Hz), 16.6 (d, J = 1.1 Hz), 26.6 (d, J = 1.5 Hz), 30.8 (d, J = 2.7 Hz), 32.5 (d, J = 4.2 Hz), 58.6 (d, J = 140.2 Hz), 96.8 (d, J = 286.9 Hz), 126.2, 128.4, 128.6, 140.6; ^{19}F NMR (188 MHz, CDCl_3) major isomer: δ = -154.9 ; minor isomer: δ = -131.7 ; IR (neat) 3029, 2955, 2932, 2861, 1605, 1497, 1472, 1366, 1254, 1127, 1086, 1009, 957, 891, 841, 824, 808, 781, 749, 698, 681 cm^{-1} . Found: C, 68.75; H, 9.17%. Calcd for $\text{C}_{17}\text{H}_{27}\text{FOSi}$: C, 68.52; H, 8.98%.

1-*t*-Butyldimethylsilyl-1,2-epoxy-1-fluorononane (7d): Obtained in 97% yield as a 56 : 44 mixture of stereoisomers. A colorless oil, R_f 0.40 (hexane–ethyl acetate = 5 : 1). ^1H NMR (200 MHz, CDCl_3) major isomer: δ = 0.05 (s, 3H), 0.11 (s, 3H), 0.80–1.10 (m, 12H), 1.15–1.80 (m, 12H), 2.93–3.05 (m, 1H); minor isomer: (assignable peak) δ = 2.59 (t, J = 5.9 Hz, 1H); ^{13}C NMR (50 MHz, CDCl_3) major isomer: (assignable peaks) δ = -8.6 (d, J = 2.3 Hz), -6.4 (d, J = 4.2 Hz), 14.0, 16.6 (d, J = 1.1 Hz), 22.6, 31.7, 60.6 (d, J = 20.1 Hz), 96.7 (d, J = 285.8 Hz); minor isomer: (assignable peaks) δ = -8.2 (d, J = 3.0 Hz), -7.0 (d, J = 3.0 Hz), 16.5, 22.6, 31.7, 57.6 (d, J = 16.7 Hz), 96.3 (d, J = 294.2 Hz); ^{19}F NMR (188 MHz, CDCl_3) major isomer: δ = -132.0 ; minor isomer: δ = -155.5 ; IR (neat) 2957, 2930, 2859, 1466, 1366, 1254, 961,

841, 826, 810, 779, 681 cm^{-1} ; MS m/z (rel intensity) 276 ($M^+ + 2$, 0.9), 275 ($M^+ + 1$, 1.6), 274 (M^+ , 6.5), 133 (100). HRMS Found: m/z 274.2115. Calcd for $\text{C}_{15}\text{H}_{30}\text{OFSi}$: M , 274.2128.

1-*t*-Butyldimethyl[6-*t*-butyl-2-fluoro-1-oxaspiro[2.5]oct-2-yl]silane (7e):

This epoxide was isolated in 98% yield as a 73 : 27 mixture of isomers. A colorless oil, R_f 0.43 (hexane–ethyl acetate = 20 : 1). ^1H NMR (200 MHz, CDCl_3) major isomer: δ = 0.16 (s, 3H), 0.18 (s, 3H), 0.875 (s, 9H), 1.04 (s, 9H), 1.10–2.00 (m, 9H); minor isomer: δ = 0.11 (s, 3H), 0.24 (s, 3H), 0.876 (s, 9H), 1.01 (d, J = 4.3 Hz, 9H), 1.08–1.95 (m, 9H); ^{13}C NMR (50 MHz, C_6D_6) major isomer: (assignable peak) δ = –6.2 (d, J = 3.8 Hz), –5.7 (d, J = 3.8 Hz), 17.1 (d, J = 1.5 Hz), 47.1, 101.3 (d, J = 288.7 Hz); minor isomer: (assignable peaks) δ = –6.5 (d, J = 2.7 Hz), –5.5 (d, J = 5.3 Hz), 16.7, 47.9, 101.4 (d, J = 287.2 Hz); ^{19}F NMR (188 MHz, CDCl_3) major isomer: δ = –139.0; minor isomer: δ = –141.7; IR (neat) 2950, 2860, 1470, 1450, 1410, 1390, 1365, 1250, 1210, 1030, 985, 910, 905, 885, 840, 820, 805, 780, 680, 570 cm^{-1} . Found: C, 67.94; H, 11.07%. Calcd for $\text{C}_{17}\text{H}_{33}\text{FOSi}$: C, 68.03; H, 10.77%.

1-*t*-Butyldimethyl[2-fluoro-1-oxaspiro[2.5]oct-2-yl]silane (7f):

This oxirane was isolated in 97% yield as a colorless oil, R_f 0.77 (hexane–ethyl acetate = 5 : 1). ^1H NMR (200 MHz, CDCl_3) δ = 0.13 (d, J = 0.2 Hz, 3H), 0.18 (s, 3H), 1.01 (d, J = 0.1 Hz, 9H), 1.30–1.85 (m, 10H); ^{13}C NMR (50 MHz, C_6D_6) δ = –6.3 (d, J = 3.4 Hz), –5.7 (d, J = 4.2 Hz), 16.9, 24.6, 24.9, 25.9, 26.9, 31.7 (d, J = 3.4 Hz), 64.8 (d, J = 17.0 Hz), 101.5 (d, J = 287.9 Hz); ^{19}F NMR (188 MHz, CDCl_3) δ = –140.7; IR (neat) 2934, 2861, 2361, 2342, 1802, 1649, 1584, 1464, 1451, 1364, 1250, 1167, 1134, 1075, 1017, 957, 905, 891, 864, 839, 773, 675 cm^{-1} ; MS m/z (rel intensity) 246 ($M^+ + 2$, 0.3), 245 ($M^+ + 1$, 0.6), 244 (M^+ , 2.3), 226 (45), 169 (97), 75 (100). HRMS Found: m/z 244.1652. Calcd for $\text{C}_{13}\text{H}_{25}\text{OFSi}$: M , 244.1659.

1-*t*-Butyldimethylsilyl-1,2-epoxy-1-fluoro-2,2-diphenylethane (7g):

Isolated in 89% yield as a colorless oil, R_f 0.68 (hexane–ethyl acetate = 5 : 1). ^1H NMR (200 MHz, CDCl_3) δ = –0.37 (s, 3H), –0.12 (s, 3H), 1.01 (s, 9H), 7.20–7.55 (m, 10H); ^{13}C NMR (50 MHz, CDCl_3) δ = –7.4 (d, J = 4.2 Hz), –7.0 (d, J = 2.3 Hz), 17.1 (d, J = 1.9 Hz), 26.8 (d, J = 1.9 Hz), 67.3 (d, J = 17.8 Hz), 100.5 (d, J = 299.4 Hz), 127.2 (d, J = 1.1 Hz), 127.6 (d, J = 1.5 Hz), 127.7, 127.9, 128.1, 128.2, 137.6 (d, J = 4.2 Hz), 137.9 (d, J = 3.8 Hz); ^{19}F NMR (188 MHz, CDCl_3) δ = –132.5; IR (neat) 3063, 3033, 2932, 2861, 1813, 1497, 1472, 1449, 1364, 1254, 1051, 926, 905, 876, 839, 808, 783, 754, 702 cm^{-1} ; MS m/z (rel intensity) 329 ($M^+ + 1$, 0.3), 328 (M^+ , 0.8), 253 (0.4), 214 (0.2), 194 (19), 166 (100), 77 (39). Found: C, 73.09; H, 7.73%. Calcd for $\text{C}_{20}\text{H}_{25}\text{FOSi}$: C, 73.13; H, 7.67%.

Alkylation of 6

To a THF (2 ml) solution of **3** (181 mg, 0.59 mmol) was added a 1.49 M hexane solution of butyllithium (0.40 ml, 0.59 mmol) at –98 °C. The resulting solution was stirred for 0.5 h at –98 °C. An alkylating agent (0.4 mmol) in THF (1.0 ml) was added slowly to the reaction mixture. After 0.5 h, the reaction mixture was quenched with a sat. NH_4Cl aq. solution and extracted with diethyl ether (20 ml x 3); the combined organic layer was dried over anhydrous sodium sulfate. Concentration *in vacuo* gave a crude product, which was purified by silica-gel column chromatography to afford analytically pure samples of **10**.

1-Bromo-1-(*t*-butyldimethylsilyl)-1-fluoroethane (10a): Obtained in 70% yield as a colorless oil, R_f 0.78 (hexane). ^1H NMR (200 MHz, CDCl_3) δ = 0.18 (s, 3H), 0.24 (s, 3H), 1.02 (d, J = 2.6 Hz, 9H), 2.20 (d, J = 24.2 Hz, 3H); ^{13}C NMR (50 MHz, CDCl_3) δ = –7.0 (d, J = 2.7 Hz), –6.9 (d, J = 1.5 Hz), 17.8, 27.4 (d, J = 1.1 Hz), 29.7 (d, J = 20.6 Hz), 112.2 (d, J = 264.7 Hz); ^{19}F NMR (188 MHz, CDCl_3) δ = –115.3 (d, J = 24.2 Hz); IR (neat) 2960, 2930, 2850, 1460, 1370, 1250, 1150, 1075, 1040, 1000, 895, 840, 820, 775, 690, 670, 570 cm^{-1} ; MS m/z (rel intensity) 161 ($M^+ - \text{Br}$, 1.6), 143 (24), 141 (24), 125 (29), 115 (6), 77 (100), 73 (65), 57 (96). HRMS Found: m/z 161.1153. Calcd for $\text{C}_8\text{H}_{18}\text{FSi}$: $M^+ - \text{Br}$, 161.1162.

1-Bromo-1-(*t*-butyldimethylsilyl)-1-fluoropropane (10b): Isolated in 85% yield as a colorless oil, R_f 0.61 (hexane). ^1H NMR (200 MHz, CDCl_3) δ = 0.19 (s, 3H), 0.25 (s, 3H), 1.03 (d, J = 0.6 Hz, 9H), 1.19 (t, J = 7.2 Hz, 3H), 1.92–2.42 (m, 2H); ^{13}C NMR (50 MHz, CDCl_3) δ = –6.6 (d, J = 2.7 Hz), –6.5 (d, J = 1.5 Hz), 8.7 (d, J = 7.6 Hz), 17.9, 27.5 (d, J = 1.1 Hz), 35.6 (d, J = 19.3 Hz), 117.9 (d, J = 266.8 Hz); ^{19}F NMR (188 MHz, CDCl_3) δ = –125.8 (dd, J = 10.2, 33.9 Hz); IR (neat) 2963, 2934, 2886, 2863, 1472, 1464, 1395, 1366, 1252, 1111, 1076, 1007, 965, 839, 801, 777, 725, 673 cm^{-1} . Found: C, 42.56; H, 7.98%. Calcd for $\text{C}_9\text{H}_{20}\text{FOSi}$: C, 42.35; H, 7.90%.

1-Bromo-1-(*t*-butyldimethylsilyl)-1-fluoro-2-phenylethane (10c): This was isolated in 62% yield as a colorless oil, R_f 0.39 (hexane). ^1H NMR (200 MHz, CDCl_3) δ = 0.25 (s, 3H), 0.28 (s, 3H), 1.11 (d, J = 0.6 Hz, 9H), 3.22 (dd, J = 14.7, 39.7 Hz, 1H), 3.69 (dd, J = 9.8, 14.5 Hz, 1H), 7.26–7.43 (m, 5H); ^{13}C NMR (50 MHz, CDCl_3) δ = –6.7 (d, J = 2.3 Hz), –6.5 (d, J = 1.5 Hz), 18.1, 27.7 (d, J = 1.1 Hz), 47.5 (d, J = 18.3 Hz), 113.7 (d, J = 269.2 Hz), 127.2, 127.9, 131.2 (d, J = 1.5 Hz), 134.9 (d, J = 2.3 Hz); ^{19}F NMR (188 MHz, CDCl_3) δ = –127.6; IR (neat) 3088, 3065, 3034, 2961, 2932, 2886, 2861, 1605, 1497, 1472, 1464, 1456, 1414, 1395, 1366, 1254, 1208, 1046, 1030, 1009, 995, 932, 839, 824, 812, 779, 729, 696, 673, 590, 567 cm^{-1} .

Found: C, 52.85; H, 7.03%. Calcd for $C_{14}H_{22}BrFSi$: C, 52.99; H, 6.99%.

1-Bromo-1-(*t*-butyldimethylsilyl)-1-fluorobut-3-ene (10d): Obtained in 69% yield as a colorless oil, R_f 0.56 (hexane). 1H NMR (200 MHz, $CDCl_3$) δ = 0.20 (s, 3H), 0.25 (s, 3H), 1.04 (s, 9H), 2.70–3.20 (m, 2H), 5.10–5.35 (m, 2H), 5.90–6.10 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ = –6.6 (d, J = 2.3 Hz), –6.9 (d, J = 2.0 Hz), 17.9, 27.5, 46.8 (d, J = 19.0 Hz), 114.3 (d, J = 267.1 Hz), 119.5, 131.6 (d, J = 7.6 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) δ = –125.0 (dd, J = 10.2, 30.5 Hz); IR (neat) 3083, 2963, 2932, 2863, 1642, 1472, 1466, 1410, 1395, 1366, 1254, 1235, 1134, 1057, 1007, 990, 922, 839, 826, 777, 673, 629 cm^{-1} ; MS m/z (rel intensity) 187 (M^+ –Br, 1), 151 (0.4), 139 (28), 137 (28), 115 (18), 77 (73), 57 (100). HRMS Found: m/z 187.1322. Calcd for $C_{10}H_{20}FSi$: M^+ –Br, 187.1318.

1-Bromo-1-(*t*-butyldimethylsilyl)-1-fluoro-4-methylpent-3-ene (10e): This product was isolated in 66% yield as a colorless oil, R_f 0.69 (hexane). 1H NMR (200 MHz, $CDCl_3$) δ = 0.20 (s, 3H), 0.24 (s, 3H), 1.03 (s, 9H), 1.64 (s, 3H), 1.78 (d, J = 1.2 Hz, 3H), 2.67–3.14 (m, 2H), 5.32–5.43 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ = –6.6 (d, J = 2.7 Hz), –6.3 (d, J = 1.9 Hz), 17.9, 18.4 (d, J = 0.8 Hz), 25.9, 27.5 (d, J = 1.1 Hz), 41.3 (d, J = 19.0 Hz), 116.0 (d, J = 266.8 Hz), 117.5 (d, J = 6.8 Hz), 135.8; ^{19}F NMR (188 MHz, $CDCl_3$, 188 MHz) δ = –124.2 (dd, J = 11.9, 32.2 Hz); IR (neat) 2965, 2932, 2886, 2861, 1676, 1472, 1464, 1451, 1414, 1377, 1366, 1254, 1181, 1113, 1046, 936, 839, 823, 812, 777, 739, 673 cm^{-1} ; MS m/z (rel intensity) 181 (M^+ +2–SiMe₂(*t*-Bu), 0.4), 179 (M^+ –SiMe₂(*t*-Bu), 0.3), 160 (0.7), 139 (22), 137 (22), 115 (9), 77 (100), 57 (35). HRMS Found: m/z 178.9980. Calcd for C_6H_9BrF : M^+ –Si(*t*-Bu)Me₂, 178.9872.

1-Bromo-1-(*t*-butyldimethylsilyl)-1-fluoro-4-phenylbutane (10f): This was prepared in 83% yield as a colorless oil, R_f 0.50 (hexane). 1H NMR (200 MHz, $CDCl_3$) δ = 0.16 (s, 3H), 0.22 (s, 3H), 0.99 (d, J = 0.6 Hz, 9H), 1.90–2.35 (m, 4H), 2.68 (t, J = 6.6 Hz, 2H), 7.05–7.35 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ = –6.6 (d, J = 3.0 Hz), –6.5 (d, J = 1.9 Hz), 17.9, 26.0 (d, J = 5.7 Hz), 27.5 (d, J = 0.8 Hz), 35.4, 41.9 (d, J = 19.0 Hz), 116.9 (d, J = 266.5 Hz), 125.9, 128.4 (2 peaks), 141.7; ^{19}F NMR (188 MHz, $CDCl_3$) δ = –123.9 (dd, J = 6.6, 30.5 Hz); IR (neat) 3029, 2959, 2932, 2861, 1605, 1497, 1472, 1464, 1366, 1254, 1084, 1007, 955, 839, 810, 777, 747 cm^{-1} . Found: C, 55.51; H, 7.63%. Calcd for $C_{16}H_{26}BrFSi$: C, 55.64; H, 7.59%.

1-Bromo-1-(*t*-butyldimethylsilyl)-1-fluorohex-5-ene (10g): Obtained in 90 % yield as a colorless oil, R_f 0.65 (hexane). 1H NMR (200 MHz, $CDCl_3$) δ = 0.19 (s, 3H), 0.24 (s, 3H), 1.02 (s, 9H), 1.70–2.35 (m, 6H), 4.90–5.22 (m, 2H), 5.82 (ddt, J = 10.2, 17.0, 6.6 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ = –6.6 (d, J = 2.7 Hz), –6.5

(d, J = 1.5 Hz), 17.9, 23.5 (d, J = 5.7 Hz), 27.5 (d, J = 1.1 Hz), 33.3, 41.7 (d, J = 18.6 Hz), 115.1, 117.0 (d, J = 266.4 Hz), 138.03; ^{19}F NMR (188 MHz, $CDCl_3$) δ = –124.1 (dd, J = 10.2, 33.9 Hz); IR (neat) 3079, 2959, 2934, 2861, 1642, 1509, 1474, 1464, 1366, 1254, 949, 912, 839, 824, 777, 673 cm^{-1} ; MS m/z (rel intensity) 181 (M^+ +2–Si(*t*-Bu)Me₂, 0.7), 179 (M^+ –SiMe₂(*t*-Bu), 0.7), 159 (0.5), 139 (52), 137 (52), 115 (15), 77 (100), 73 (97), 57 (100). HRMS Found: m/z 178.9885. Calcd for C_6H_9BrF : M^+ –Si(*t*-Bu)Me₂, 178.9872.

Bromo(*t*-butyldimethylsilyl)fluoro(trimethylsilyl)methane (10h): This product was isolated in 74% yield as a colorless oil, R_f 0.58 (hexane). 1H NMR (200 MHz, $CDCl_3$) δ = 0.18 (s, 3H), 0.19 (s, 3H), 0.25 (s, 9H), 1.06 (d, J = 0.6 Hz, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ = –5.0 (d, J = 1.1 Hz), –4.9 (d, J = 4.2 Hz), –2.0 (d, J = 2.3 Hz), 18.9 (d, J = 0.8 Hz), 113.9 (d, J = 264.3 Hz); ^{19}F NMR (188 MHz, $CDCl_3$, 188 MHz) δ = –169.7. IR (neat) 2959, 2932, 2861, 2361, 1474, 1464, 1412, 1366, 1254, 949, 885, 847, 804, 787, 776, 745, 702, 619 cm^{-1} ; MS m/z (rel intensity) 302 (M^+ +4, 0.01), 301 (M^+ +3, 0.02), 300 (M^+ +2, 0.07), 299 (M^+ +1, 0.01), 298 (M^+ , 0.05), 151 (46), 149 (45), 139 (58), 137 (58), 85 (57), 73 (100), 57 (81). Found: C, 39.97; H, 7.83%. Calcd for $C_{10}H_{24}BrFSi_2$: C, 40.12; H, 8.08%.

Bis(trimethylsilyl)fluoro(tributylstannyl)methane (11)

To a mixture of **4** (87 mg, 0.34 mmol) and Bu_3SnCl (0.11 ml, 0.41 mmol) in THF (2 ml)– Et_2O (1 ml) was added a 0.98 M cyclohexane solution of *s*-butyllithium (0.36 ml, 0.35 mmol) dropwise at –130 °C under an argon atmosphere. The resulting mixture was stirred for 30 min at –130 °C, gradually warmed to room temperature, and stirred for 12 h before quenching with sat. aq. NH_4Cl solution (5 ml). The organic layer was separated; the aqueous layer was extracted with Et_2O (20 ml x 3). The combined organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to afford an oil which was purified by column chromatography (hexane) to give **11** (107 mg, 68% yield as a colorless oil. R_f 0.56 (hexane). 1H NMR (300 MHz, $CDCl_3$) δ = 0.11 (s, 18H), 0.90 (t, J = 7.5 Hz, 9H), 0.96–1.20 (m, 6H), 1.33 (q, J = 7.2 Hz, 6H), 1.42–1.55 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = –0.4 (d, J = 4.0 Hz), 11.5 (d, J = 4.0 Hz), 13.6, 27.6, 29.2, 105.8; ^{19}F NMR (188 MHz, $CDCl_3$) δ = –263.7 (t, J = 76.1 Hz); IR (neat) 2960, 2920, 2850, 1460, 1420, 1375, 1070, 960, 880, 840, 760, 670, 590 cm^{-1} . Found: C, 48.96; H, 9.88%. Calcd for $C_{19}H_{45}FSi_2Sn$: C, 48.82; H, 9.70%.

One-pot preparation of 11:

A 1.52 M hexane solution of butyllithium (6.6 ml, 10 mmol) was added to a solution of tribromofluoromethane (0.49 ml, 5.0 mmol) and Me_3SiCl (1.27 ml, 10 mmol) in THF (10 ml)– Et_2O (5 ml) at -130°C via syringe over a period of 10 min. The mixture was stirred for 30 min; Bu_3SnCl (1.49 ml, 5.5 mmol) and a 0.74 M cyclohexane solution of *s*-BuLi (6.76 ml, 5.0 mmol) were successively added to the reaction mixture at -130°C . The resulting solution was stirred for 30 min at -130°C before quenching with sat. aq. NH_4Cl solution (30 ml). The organic layer was separated; the aqueous layer was extracted with Et_2O (40 ml x 3). The combined organic extracts were dried over anhydrous MgSO_4 and concentrated *in vacuo*. The residue was purified by column chromatography to afford **11** (1.56 g, 67% yield).

General Procedure for Reaction of 11 with Aldehyde

To a solution of **11** in THF (2 ml) was added butyllithium (1.05 mmol) at -78°C ; the resulting mixture was stirred for 20 min at -78°C . An aldehyde (1.2 mmol) was added to the reagent solution at -98°C , and the resulting mixture was allowed to warm to room temperature before quenching with sat. aq. NH_4Cl solution. The organic layer was separated; the aqueous layer was extracted with Et_2O (20 ml x 3); the combined organic layer was dried over anhydrous MgSO_4 . Concentration *in vacuo* gave an oil which was purified by column chromatography to give **12**.

1-Fluoro-2-phenyl-1-trimethylsilyl ethene (12a): This was prepared in 51% yield as a mixture of isomers (*E* : *Z* = 24 : 76). A colorless oil, R_f 0.70 (hexane). ^1H NMR (200 MHz, CDCl_3) (*Z*)-isomer: δ = -0.03 (s, 9H), 7.04 (d, J = 35.0 Hz, 1H), 6.98–7.49 (m, 5H), (*E*)-isomer: δ = 0.24 (s, 9H), 5.85 (d, J = 52.2 Hz, 1H); ^{19}F NMR (188 MHz, CDCl_3) (*Z*)-isomer: δ = -106.6 (d, J = 35.0 Hz), (*E*)-isomer: δ = -114.0 (d, J = 52.2 Hz); IR (neat) 2960, 2930, 2850, 1460, 1330, 1250, 840, 665 cm^{-1} ; MS m/z (rel intensity) 196 ($\text{M}^+ + 2$, 3), 195 ($\text{M}^+ + 1$, 10), 194 (M^+ , 60), 77 (100). HRMS Found: m/z 194.0920. Calcd for $\text{C}_{17}\text{H}_{17}\text{FO}$: M, 194.0927.

1-Fluoro-2-(4-methylphenyl)-1-trimethylsilyl ethene (12b): This olefin was prepared in 69% yield as an *E* : *Z* = 24 : 76 mixture of stereoisomers. A colorless oil, R_f 0.67 (hexane). ^1H NMR (200 MHz, CDCl_3) (*Z*)-isomer: δ = 0.09 (s, 9H), 2.35 (s, 3H), 7.03 (d, J = 38.8 Hz, 1H), 7.08–7.50 (m, 4H), (*E*)-isomer: δ = 0.25 (s, 9H), 5.83 (d, J = 52.6 Hz, 1H); ^{19}F NMR (188 MHz, CDCl_3) (*Z*)-isomer: δ = -107.5 (d, J = 38.8 Hz), (*E*)-isomer: δ = -115.3 (d, J = 52.6 Hz); IR (neat) 3025, 2960, 1510, 1250, 1040, 850, 810, 760 cm^{-1} ; MS m/z (rel intensity) 210 ($\text{M}^+ + 2$, 5), 209 ($\text{M}^+ + 1$, 21), 208 (M^+ , 100). HRMS Found: m/z 208.1083. Calcd for $\text{C}_{12}\text{H}_{17}\text{FSi}$: M, 208.1084.

1-Fluoro-2-(4-methoxyphenyl)-1-trimethylsilyl ethene (12c): Isolated in 98% yield as a mixture of isomers (*E* : *Z* = 15 : 85). A colorless oil, R_f 0.24 (hexane). ^1H NMR (200 MHz, CDCl_3) (*Z*)-isomer: δ = 0.08 (s, 9H), 3.81 (s, 3H), 6.80–7.60 (m, 5H), (*E*)-isomer: δ = 0.24 (s, 9H), 5.79 (d, J = 52.6 Hz, 1H); ^{19}F NMR (188 MHz, CDCl_3) (*Z*)-isomer: δ = -108.2 (d, J = 35.2 Hz), (*E*)-isomer: δ = -117.6 (d, J = 51.9 Hz); IR (neat) 2980, 2950, 1600, 1500, 1245, 1170, 1030, 840, 750 cm^{-1} ; MS m/z (rel intensity) 226 ($\text{M}^+ + 2$, 5), 225 ($\text{M}^+ + 1$, 19), 224 (M^+ , 100). HRMS Found: m/z 224.1036. Calcd for $\text{C}_{12}\text{H}_{17}\text{FOSi}$: M, 224.1033.

1-Fluoro-2-(4-phenylphenyl)-1-trimethylsilyl ethene (12d): Prepared in 87% yield as a mixture of stereoisomers (*E* : *Z* = 28 : 72). A colorless oil, R_f 0.67 (hexane). ^1H NMR (200 MHz, CDCl_3) (*Z*)-isomer: δ = 0.13 (s, 9H), 7.06 (d, J = 35.2 Hz, 1H), 7.22–7.80 (m, 9H), (*E*)-isomer: δ = 0.27 (s, 9H), 5.90 (d, J = 52.0 Hz, 1H); ^{19}F NMR (188 MHz, CDCl_3) (*Z*)-isomer: δ = -105.8 (d, J = 35.2 Hz), (*E*)-isomer: δ = -113.4 (d, J = 52.0 Hz); IR (neat) 2960, 2930, 1490, 1460, 1250, 1040, 850, 760, 700 cm^{-1} ; MS m/z (rel intensity) 272 ($\text{M}^+ + 2$, 11), 271 ($\text{M}^+ + 1$, 41), 270 (M^+ , 100). HRMS Found: m/z 270.1230. Calcd for $\text{C}_{12}\text{H}_{17}\text{FSi}$: M, 270.1240.

1-Fluoro-4-phenyl-1-trimethylsilyl-1,3(*E*)-butadiene (12f): Produced in 86% yield as a mixture of isomers (*E* : *Z* = 27 : 83). A pale yellow oil, R_f 0.34 (hexane). ^1H NMR (200 MHz, CDCl_3) (*Z*)-isomer: δ = 0.34 (s, 9H), 5.70–7.50 (m, 8H), (*E*)-isomer: δ = 0.22 (s, 9H); ^{19}F NMR (188 MHz, CDCl_3) (*Z*)-isomer: δ = -107.3 (d, J = 33.7 Hz), (*E*)-isomer: δ = -116.6 (d, J = 45.7 Hz); IR (neat) 3050, 2960, 1500, 1450, 1250, 1040, 960, 840, 750, 690 cm^{-1} ; MS m/z (rel intensity) 222 ($\text{M}^+ + 2$, 5), 221 ($\text{M}^+ + 1$, 21), 220 (M^+ , 100). HRMS Found: m/z 220.1087. Calcd for $\text{C}_{12}\text{H}_{14}\text{F}_4\text{Si}$: M, 220.1084.

1-Fluoro-4-phenyl-1-trimethylsilyl-1-butene (12g): Prepared in 75% yield as a 93 : 7 mixture of *EZ* isomers. A colorless oil, R_f 0.34 (hexane). ^1H NMR (200 MHz, CDCl_3) (*E*)-isomer: δ = 0.13 (s, 9H), 2.30–2.70 (m, 4H), 5.06 (dt, J = 49.6, 7.4 Hz, 1H), 7.10–7.40 (m, 5H), (*Z*)-isomer: δ = 0.17 (s, 9H), 5.86 (dt, J = 36.8, 8.4 Hz, 1H); ^{13}C NMR (50 MHz, CDCl_3) (*E*)-isomer: δ = -2.6 (d, J = 1.1 Hz), 25.3 (d, J = 10.7 Hz), 35.3, 120.7 (d, J = 4.2 Hz), 125.9, 128.3, 128.4, 141.7, 168.3 (d, J = 276.2 Hz), (*Z*)-isomer (only characteristic peaks are shown): δ = -1.5 (d, J = 3.1 Hz), 27.4 (d, J = 12.9 Hz), 36.7, 122.9 (d, J = 13.3 Hz), 126.0, 128.4, 128.5; ^{19}F NMR (188 MHz, CDCl_3) (*E*)-isomer: δ = -123.2 (d, J = 49.6 Hz), (*Z*)-isomer: δ = -112.4 (d, J = 36.8 Hz); IR (neat) 3030, 2960, 2860, 1650, 1605, 1500, 1450, 1250, 1090, 1030, 1000, 980, 940, 840, 750, 700, 630 cm^{-1} ; MS m/z (rel intensity) 224 ($\text{M}^+ + 2$, 0.4), 223 ($\text{M}^+ + 1$, 1.4), 222 (M^+ , 7.3), 91 (100). Found: C, 70.28; H, 8.91%. Calcd for $\text{C}_{13}\text{H}_{19}\text{FSi}$: C,

70.22; H, 8.61%.

1-Fluoro-2-(pentafluorophenyl)-1-trimethylsilylethene (12h): Prepared in 53% yield as a (*E* : *Z* = >99 : <1) mixture of stereoisomer. A colorless oil, *R*_f 0.61 (hexane). ¹H NMR (200 MHz, CDCl₃) δ = 0.28 (s, 9H), 5.79 (d, *J* = 47.6 Hz, 1H); ¹⁹F NMR (188 MHz, CDCl₃) δ = -99.0 (dt, *J* = 47.6, 24.3 Hz), -138.1 (td, *J* = 22.7, 9.2 Hz), -156.2 (t, *J* = 21.4 Hz), -163.4 (td, *J* = 21.4, 7.5 Hz); IR (neat) 2970, 2930, 1660, 1520, 1500, 1255, 1130, 1080, 990, 970, 850, 760 cm⁻¹; MS *m/z* (rel intensity) 286 (*M*⁺+2, 2), 285 (*M*⁺+1, 6), 284 (*M*⁺, 35), 269 (100). HRMS Found: *m/z* 284.0460. Calcd for C₁₁H₁₀F₆Si: *M*, 284.0456.

1-Fluoro-2-(4-trifluoromethylphenyl)-1-trimethylsilylethene (12i): Prepared in 98% yield as a mixture of stereoisomer (*E* : *Z* = 57 : 43). A colorless oil, *R*_f 0.24 (hexane). ¹H NMR (200 MHz, CDCl₃) (*E*)-isomer: δ = 0.26 (s, 9H), 5.79 (d, *J* = 52.6 Hz, 1H), 7.30–7.70 (m, 4H), (*Z*)-isomer: δ = 0.09 (s, 9H), 7.01 (d, *J* = 34.8 Hz, 1H); ¹⁹F NMR (188 MHz, CDCl₃) (*E*)-isomer: δ = -63.1, -110.0 (d, *J* = 52.6 Hz), (*Z*)-isomer: δ = -63.0, -102.7 (d, *J* = 34.8 Hz); IR (neat) 2960, 1620, 1410, 1320, 1250, 1160, 1120, 1065, 1020, 850, 760 cm⁻¹; MS *m/z* (rel intensity) 264 (*M*⁺+2, 3), 263 (*M*⁺+1, 12), 262 (*M*⁺, 62), 151 (100). HRMS Found: *m/z* 262.0794. Calcd for C₁₂H₁₄F₄Si: *M*, 262.0794.

Reaction of 5 with Aldehydes. A General Procedure with KF/18-crown-6

To a DMF (2 ml) solution of KF (1.0 mmol)/18-crown-6 (1.0 mmol) were added an aldehyde (2.5 mmol) and **5** (1.0 mmol) successively at room temperature. The reaction mixture was stirred for 12 h, then quenched with 3 M HCl (5 ml), and extracted with Et₂O (20 ml x 3). The combined organic layer was washed with brine, dried over anhydrous MgSO₄, and concentrated *in vacuo*. The crude products were purified by column chromatography to give **13**.

(*E*)-2-Fluoro-1,3-diphenyl-2-propen-1-ol ((*E*)-14a): This was obtained in 48% yield as a colorless oil, *R*_f 0.53 (hexane–ethyl acetate = 4 : 1). ¹H NMR (300 MHz, CDCl₃) δ = 2.37 (brs, 1H), 5.68 (dd, *J* = 7.2, 26.7 Hz, 1H), 6.51 (d, *J* = 20.4 Hz, 1H), 7.20–7.80 (m, 10 H); ¹³C NMR (50 MHz, CDCl₃) δ = 69.2 (d, *J* = 25.7 Hz), 111.2 (d, *J* = 25.7 Hz), 126.4 (2 peaks), 127.5, 128.2, 128.6 (2 peaks), 132.6 (d, *J* = 12.6 Hz), 139.2, 159.2 (d, *J* = 256.4 Hz); ¹⁹F NMR (188 MHz, CDCl₃) δ = -120.1 (dd, *J* = 20.4, 26.7 Hz); IR (neat) 3400, 1680, 1495, 1449, 1219, 1144, 1024, 920, 893, 756, 698 cm⁻¹. Found: C, 79.14; H, 5.79%. Calcd for C₁₅H₁₃FO: C, 78.93; H, 5.74%.

(*Z*)-2-Fluoro-1,3-diphenyl-2-propen-1-ol ((*Z*)-14a): This fluoroalkyl-alcohol was prepared in 26% yield as a white solid, mp 61–62 °C; *R*_f 0.27 (hexane–ethyl

acetate = 4 : 1). ¹H NMR (300 MHz, CDCl₃) δ = 2.45 (brs, 1H), 5.33 (dd, *J* = 4.5, 12.0 Hz, 1H), 5.90 (d, *J* = 39.3 Hz, 1H), 7.20–7.60 (m, 10 H); ¹³C NMR (50 MHz, CDCl₃) δ = 73.2 (d, *J* = 32.0 Hz), 106.9 (d, *J* = 6.3 Hz), 126.8, 127.4 (d, *J* = 2.2 Hz), 128.4, 128.5, 128.6, 128.7 (d, *J* = 7.5 Hz), 132.6 (d, *J* = 2.3 Hz), 139.3, 159.2 (d, *J* = 266.6 Hz); ¹⁹F NMR (188 MHz, CDCl₃) δ = -115.6 (dd, *J* = 12.0, 39.3 Hz); IR (KBr) 3400, 1686, 1495, 1449, 1231, 1275, 1157, 1022, 895, 862, 725, 695 cm⁻¹. Found: C, 78.95; H, 5.69%. Calcd for C₁₅H₁₃FO: C, 78.93; H, 5.74%.

(*E*)-2-Fluoro-1,3-bis(4-methylphenyl)-2-propen-1-ol ((*E*)-14b): This product was prepared in 48% yield as a white solid, mp 80–81 °C; *R*_f 0.57 (hexane–ethyl acetate = 4 : 1). ¹H NMR (200 MHz, CDCl₃) δ = 2.25 (d, *J* = 11.3 Hz, 1H), 2.35 (s, 3H), 2.37 (s, 3H), 5.65 (dd, *J* = 7.5, 26.4 Hz, 1H), 6.45 (d, *J* = 20.5 Hz, 1H), 7.10–7.45 (m, 8H); ¹⁹F NMR (188 MHz, CDCl₃) δ = -120.7 (dd, *J* = 20.5, 26.4 Hz); IR (nujor) 3300, 1510, 1145, 1040, 900 cm⁻¹; MS *m/z* (rel intensity) 258 (*M*⁺+2, 2), 257 (*M*⁺+1, 18), 256 (*M*⁺, 100). HRMS Found: *m/z* 256.1255. Calcd for C₁₇H₁₇FO: *M*, 256.1263.

(*Z*)-2-Fluoro-1,3-bis(4-methylphenyl)-2-propen-1-ol ((*Z*)-14b): This adduct was prepared in 22% yield as a white solid, mp 48–49 °C; *R*_f 0.27 (hexane–ethyl acetate = 4 : 1). ¹H NMR (200 MHz, CDCl₃) δ = 2.24 (brs, 1H), 2.34 (s, 3H), 2.37 (s, 3H), 5.37 (d, *J* = 11.5 Hz, 1H), 5.87 (d, *J* = 39.3 Hz, 1H), 7.10–7.55 (m, 8H); ¹⁹F NMR (188 MHz, CDCl₃) δ = -116.5 (dd, *J* = 11.5, 39.3 Hz); IR (nujor) 3300, 1520, 1150, 1020, 810 cm⁻¹; MS *m/z* (rel intensity) 258 (*M*⁺+2, 2), 257 (*M*⁺+1, 19), 256 (*M*⁺, 100). HRMS Found: *m/z* 256.1263. Calcd for C₁₇H₁₇FO: *M*, 256.1255.

2-Fluoro-1,3-bis(4-methoxyphenyl)-2-propen-1-ol (14c): This was isolated in 78% yield as a mixture of stereoisomers (*E* : *Z* = 65 : 35). A pale yellow oil, *R*_f 0.17 (hexane–ethyl acetate = 4 : 1). ¹H NMR (300 MHz, CDCl₃) (*E*)-isomer: δ = 2.35 (brs, 1H), 3.81 (s, 3H), 3.82 (s, 3H), 5.62 (d, *J* = 26.0 Hz, 1H), 6.42 (d, *J* = 20.4 Hz, 1H), 6.85–7.50 (m, 8H), (*Z*)-isomer: δ = 5.30 (d, *J* = 11.4 Hz, 1H), 5.83 (d, *J* = 39.3 Hz, 1H); ¹⁹F NMR (188 MHz, CDCl₃) (*E*)-isomer: δ = -123.2 (dd, *J* = 20.4, 26.0 Hz), (*Z*)-isomer: δ = -118.3 (dd, *J* = 11.4, 39.3 Hz); IR (neat) 3470, 3000, 2950, 2930, 2900, 2840, 1680, 1610, 1510, 1460, 1300, 1250, 1180, 1140, 1030, 830, 755 cm⁻¹; MS *m/z* (rel intensity) 290 (*M*⁺+2, 2), 289 (*M*⁺+1, 11), 288 (*M*⁺, 49), 272 (100). HRMS Found: *m/z* 288.1186. Calcd for C₁₇H₁₇FO: *M*, 288.1162.

2-Fluoro-1,3-bis(4-phenylphenyl)-2-propen-1-ol (14d): This product was obtained in 68% yield as a mixture of isomers (*E* : *Z* = 67 : 33). A yellow solid, mp 71–72 °C; *R*_f 0.24 (hexane–ethyl acetate = 4 : 1). ¹H NMR (200 MHz, CDCl₃) (*E*)-isomer: δ = 2.10 (brs, 1H), 5.81 (d, *J* = 26.8 Hz, 1H), 6.58 (d, *J* = 20.2 Hz, 1H), 7.20–

7.90 (m, 18 H), (Z)-isomer: δ = 5.44 (d, J = 11.8 Hz, 1H), 6.02 (d, J = 38.8 Hz, 1H); ^{19}F NMR (188 MHz, CDCl_3) (*E*)-isomer: δ = -119.4 (dd, J = 20.2, 26.8 Hz), (Z)-isomer: δ = -115.1 (dd, J = 11.8, 38.8 Hz); IR (nujol) 3300, 1510, 1150, 720 cm^{-1} ; MS m/z (rel intensity) 381 ($\text{M}^+ + 1$, 2.3), 380 (M^+ , 7.2), 207 (100). HRMS Found: m/z 380.1586. Calcd for $\text{C}_{27}\text{H}_{21}\text{FO}$: M, 380.1576.

2-Fluoro-1,3-bis(1-naphtyl)-2-propen-1-ol (14e): This product was isolated in 65% yield as a mixture of stereoisomers (*E* : *Z* = 61 : 39). A yellow viscous oil, R_f 0.43 (hexane-ethyl acetate = 4 : 1). ^1H NMR (300 MHz, CDCl_3) (*E*)-isomer: δ = 2.50 (brs, 1H), 6.22 (dd, J = 17.6, 25.3 Hz, 1H), 6.96 (d, J = 19.0 Hz, 1H), 7.30–8.50 (m, 14H), (Z)-isomer: δ = 6.60 (d, J = 36.8 Hz, 1H), 7.09 (ddd, J = 1.6, 7.0, 8.6 Hz, 1H); ^{19}F NMR (188 MHz, CDCl_3) (*E*)-isomer: δ = -115.2 (dd, J = 19.0, 25.2 Hz), (Z)-isomer: δ = -113.6 (dd, J = 7.0, 36.8 Hz); IR (paraffin) 3350, 1700, 1600, 1300, 1220, 1080, 1010, 840, 780, 700 cm^{-1} ; MS m/z (rel intensity) 330 ($\text{M}^+ + 2$, 3), 329 ($\text{M}^+ + 1$, 26), 328 (M^+ , 100). HRMS Found: m/z 328.1268. Calcd for $\text{C}_{23}\text{H}_{17}\text{FO}$: M, 328.1263.

5–8 References

- 1) a) D. J. Burton and Z.-Y. Yang, *Tetrahedron*, **48**, 189 (1992); b) D. J. Burton, Z.-Y. Yang, and P. A. Morken, *Tetrahedron*, **50**, 2993 (1994).
- 2) a) M. Kuroboshi, N. Yamada, Y. Takebe, and T. Hiyama, *Synlett*, **1995**, 987; b) M. Kuroboshi, N. Yamada, Y. Takebe, and T. Hiyama, *Tetrahedron Lett.*, **36**, 6271 (1995); c) M. Shimizu, Y. Takebe, M. Kuroboshi, and T. Hiyama, *Tetrahedron Lett.*, **37**, 7387 (1996); d) M. Shimizu, N. Yamada, Y. Takebe, T. Hata, M. Kuroboshi, and T. Hiyama, *Bull. Chem. Soc., Jpn*, **71**, 2903 (1998).
- 3) a) A. R. Bassindale and P. G. Taylor, "The Chemistry of Organic Silicon Compounds," Vol. 2, ed by S. Patai and Z. Rappoport, John Wiley & Sons, Inc., New York, 1989, pp. 893-963; b) J. S. Panek, "Comprehensive Organic Synthesis," Vol. 1, ed by B. M. Trost and I. Fleming, Pergamon Press, London, 1991, pp. 579-627.
- 4) Preparations and reactions of dihalo(trialkylsilyl)methylolithiums are reported in: a) D. Seyferth, J. F. M. Armbricht, and E. M. Hanson, *J. Organomet. Chem.*, **10**, 25 (1967); b) D. Seyferth, J. R. L. Lambert, and E. M. Hanson, *J. Organomet. Chem.*, **24**, 647 (1970); c) D. Seyferth, E. M. Hanson, and J. F. M. Armbricht, *J. Organomet. Chem.*, **23**, 361 (1970); d) G. Köbrich and R. V. Nagel, *Tetrahedron Lett.*, **1970**, 4693; e) R. V. Nagel and G. Köbrich, *Tetrahedron Lett.*, **1970**, 4697; f) J. Villieras, C. Bacquet, D. Masure, and J. F. Normant, *J. Organomet. Chem.*, **50**, C7 (1973); g) J. Villieras, C. Bacquet, and J.-F. Normant, *Bull. Soc. Chim. Fr.*, **1975**, 1797; h) V. G. Fritz and U. Finke, *Z. Anorg. Allg. Chem.*, **430**, 121 (1977); i) G. L. Larson and O. Rosario, *J. Organomet. Chem.*, **168**, 13 (1979); j) A. Hosomi, M. Inaba, and H. Sakurai, *Tetrahedron Lett.*, **1983**, 4727; k) H. Shinokubo, K. Miura, K. Oshima, and K. Utimoto, *Tetrahedron Lett.*, **34**, 1951 (1993); l) H. Shinokubo, K. Oshima, and K. Utimoto, *Tetrahedron Lett.*, **35**, 3741 (1994); m) H. Shinokubo, K. Oshima, and K. Utimoto, *Chem. Lett.*, **1995**, 461; n) H. Shinokubo, K. Miura, K. Oshima, and K. Utimoto, *Tetrahedron*, **52**, 503 (1994); o) H. Shinokubo, K. Oshima, and K. Utimoto, *Tetrahedron*, **52**, 14533 (1996). An example of the reagent bearing a $\text{CF}(\text{SiR}_3)\text{Li}$ moiety : $(\text{EtO})_2\text{P}(\text{O})\text{CF}(\text{SiMe}_3)\text{Li}$ which could be prepared at -78°C and was alkylated with alkyl iodides in good yields. p) C. Patois and P. Savignac, *J. Chem. Soc., Chem. Commun.*, **1993**, 1711; q) C. Patois and P. Savignac, *Synth. Commun.*, **24**, 1317 (1994); r) J. Nieschalk, A. S. Batsanov, D. O'Hagan, and J. A. K. Howard, *Tetrahedron*, **52**, 165 (1996).
- 5) a) H. Sakurai, K.-i. Nishiwaki, and M. Kira, *Tetrahedron Lett.*, **1973**, 4193; b) B.-

- T. Grobel and D. Seebach, *Angew. Chem. Int. Ed. Engl.*, **13**, 83 (1974); c) B.-T. Grobel and D. Seebach, *Chem. Ber.*, **110**, 852 (1977); d) D. Seyferth, J. L. Lefferts, and J. R. L. Lambert, *J. Organomet. Chem.*, **142**, 39 (1977); e) I. Fleming and C. D. Floyd, *J. Chem. Soc., Perkin Trans. 1*, **1981**, 969; f) D. J. Ager, *J. Org. Chem.*, **49**, 168 (1984); g) R. K. Boeckman, Jr., and R. L. Chinn, *Tetrahedron Lett.*, **26**, 5005 (1985); h) P. F. Hudrlik, E. L. O. Agwaramgbo, and A. M. Hudrlik, *J. Org. Chem.*, **54**, 5613 (1989); i) C. Palomo, J. M. Aizpurua, J. M. Garcia, I. Ganboa, F. P. Cossio, B. Lecea, and C. Lopez, *J. Org. Chem.*, **55**, 2498 (1990).
- 6) O. Yokokoji, T. Shimizu, and S. Kumai, JP 08040952, **1996**.
 - 7) a) T. Allmendinger, E. Felder, and E. Hungerbuehler, "Selective Fluorination in Organic and Bioorganic Chemistry," ed. by J. T. Welch, American Chemical Society, Washington, DC, 1991, p 186; b) J. T. Welch, J. Lin, L. G. Boros, B. DeCorte, K. Bergmann, and R. Gimi, "Biomedical Frontiers of Fluorine Chemistry," ed. by I. Ojima, J. R. McCarthy, and J. T. Welch, American Chemical Society, Washington, DC, 1996, p 129-142.
 - 8) a) P. Bey, J. R. McCarthy, and I. A. McDolanld, "Selective Fluorination in Organic and Bioorganic Chemistry," ed. by J. T. Welch, American Chemical Society, Washington, DC, 1991, p 105; b) J. R. McCarthy, P. S. Sunkara, D. P. Matthews, A. J. Bitonti, E. T. Jarvi, J. S. Sabol, R. J. Resvick, E. W. Huber, W. A. V. D. Donk, G. Yu, and J. Stubbe, "Biomedical Frontiers of Fluorine Chemistry," ed. by I. Ojima, J. R. McCarthy, and J. T. Welch, American Chemical Society, Washington, DC, 1996, p 246-264.
 - 9) H. Bürger, and P. Moritz, *Organometallics*, **12**, 4930 (1993).
 - 10) Although 1,2-difluoro-1-silyloxiranes and 1,2,2-trifluoro-1-silyloxirane were reportedly prepared by the epoxidation of the corresponding fluorosilylenes (*vide infra*), the synthesis of 1-fluoro-1-silyloxiranes has never been reported to the best of our knowledge. a) T. Dubuffet, R. Sauvetre, and J. -F. Normant, *J. Organomet. Chem.*, **354**, 1 (1988); b) A. Arnone, D. D. DesMarteau, B. Novo, V. A. Petrov, M. Pregnotato, and G. Resnati, *J. Org. Chem.* **61**, 8805 (1996).
 - 11) No product resulting from the Peterson elimination or the Brook rearrangement of **8** was observed.
 - 12) Reviews: a) A. S. Rao, S. K. Paknikar, and J. G. Kirtane, *Tetrahedron*, **39**, 2323 (1983); b) J. G. Smith, *Synthesis*, **1984**, 627.
 - 13) Reviews on the organofluorine chemistry: a) "Fluorine-Containing Molecules. Structure, Reactivity, Synthesis, and Applications," ed. by J. F. Liebman, A.

- Greenberg, and W. R. Dolbier, VCH, New York, **1988**; b) "Selective Fluorination in Organic and Bioorganic Chemistry," ed. by J. T. Welch, American Chemical Society, Washington, DC, **1991**; c) "Organofluorine Chemistry. Principles and Commercial Applications," ed. by R. E. Banks, B. E. Smart, and J. C. Tatlow, Plenum Press, New York, **1994**; d) "Chemistry of Organic Fluorine Compounds II. A Critical Review," ed. by M. Hudlicky and A. E. Pavlath, American Chemical Society, Washington, DC, (1995); e) "Synthetic Organofluorine Chemistry: Principles and Applications," ed by T. Hiyama, Springer-Verlag, *in press*.
- 14) H. Millauer, W. Schwertfeger, and G. Siegemund, *Angew. Chem. Int. Ed Engl.*, **24**, 161 (1985).
 - 15) B. E. Smart, "Organofluorine Chemistry-Principles and Commercial Applications," ed by R. E. Banks, B. E. Smart, and J. C. Tatlow, Plenum Press, New York, **1994**, pp. 57-88.
 - 16) a) I. Fleming, "Comprehensive Organic Chemistry," Vol. 3, ed by D. Barton and W. D. Ollis, Pergamon Press, Oxford, **1979**, pp. 541-686; b) Ref. 5a; pp. 951-955.
 - 17) When isopropyl iodide or isobutyl iodide was used, protonated product of **6** formed which might have resulted from a proton abstraction from the iodide.
 - 18) a) T. Hiyama, K. Nishide, and M. Obayashi, *Chem. Lett.*, **1984** 1765; b) S. Martin, R. Sauvetre, and J.-F. Normant, *J. Organomet. Chem.*, **264**, 155 (1984); c) S. Martin, R. Sauvetre, and J.-F. Normant, *J. Organomet. Chem.*, **303**, 317 (1986); d) P. Martinet, R. Sauvetre, and J.-F. Normant, *Bull. Soc. Chim. Fr.*, **127**, 86 (1990); e) S. A. Fontana, C. R. Davis, Y.-B. He, and D. J. Burton, *Tetrahedron*, **52**, 37 (1996); f) L. Xue, L. Lu, S. D. P. Q. Liu, R. M. Narske, and D. J. Burton, *J. Org. Chem.*, **62**, 1064 (1997); g) F. Tellier, M. Audouin, M. Baudry, and R. Sauvetre, *Tetrahedron Lett.*, **39**, 5041 (1998).
 - 19) When BuLi or *t*-BuLi was employed instead of *s*-BuLi, fluorostannylmethane **3** was produced in 12 or 26% yield, respectively.

List of publication

Chapter 2

- “Generation and Aldehyde Addition of a Zinc Carbenoid Substituted by Fluorine” T. Hata, M. Shimizu, and T. Hiyama, *Synlett* **1996**, 831.
- “Generation and Carbonyl Addition Reactions of Dibromofluoromethylithium Derived from Tribromofluoromethane as Applied to the Stereoselective Synthesis of Fluoro Olefins and 2-Bromo-2-fluoro-1,3-alkanediols” M. Shimizu, N. Yamada, Y. Takebe, T. Hata, M. Kuroboshi, and T. Hiyama, *Bull. Chem. Soc. Jpn.*, **71**, 2903 (1998).
- “Generation of EtZnCFBr₂ from Tribromofluoromethane and Diethylzinc and Its Chemoselective Aldehyde Addition” T. Hata, H. Kitagawa, M. Shimizu, and T. Hiyama, submitted for publication.

Chapter 3

- “Generation and Carbonyl Addition Reactions of Dibromofluoromethylithium Derived from Tribromofluoromethane as Applied to the Stereoselective Synthesis of Fluoro Olefins and 2-Bromo-2-fluoro-1,3-alkanediols” M. Shimizu, N. Yamada, Y. Takebe, T. Hata, M. Kuroboshi, and T. Hiyama, *Bull. Chem. Soc. Jpn.*, **71**, 2903 (1998).

Chapter 4

- “Generation and Carbonyl Addition Reactions of Dibromofluoromethylithium Derived from Tribromofluoromethane as Applied to the Stereoselective Synthesis of Fluoro Olefins and 2-Bromo-2-fluoro-1,3-alkanediols” M. Shimizu, N. Yamada, Y. Takebe, T. Hata, M. Kuroboshi, and T. Hiyama, *Bull. Chem. Soc. Jpn.*, **71**, 2903 (1998).

Chapter 5

- “Bromo(*t*-butyldimethylsilyl)fluoromethylithium: A Fluorinated Nucleophilic Carbenoid Reagent Stabilized by a Silyl Substituent” M. Shimizu, T. Hata, and T. Hiyama, *Tetrahedron Lett.*, **38**, 4591 (1997).
- “Novel Synthesis of 1-Fluoro-1-Silyloxiranes Using Bromo(*t*-butyldimethylsilyl)fluoromethylithium and Carbonyl Compounds” M. Shimizu, T. Hata, and T. Hiyama, *Heterocycles*, *in press*.
- “FC(SiMe₃)₃ and FC(SiMe₃)₂SnBu₃: A Novel C₁ Building Block for Fluoro Olefins” M. Shimizu, T. Hata, and T. Hiyama, *Tetrahedron Lett.*, **40**, 7375 (1999).
- “An Organometallic Route from Polyhalofluoroalkanes to Bioactive Molecules. FC(SiMe₃)₃ and FC(SiMe₃)₂SnBu₃: A Novel C₁ Building Block for Fluoro Olefins” M. Shimizu, T. Hata, and T. Hiyama, submitted for publication.

Other publications

- “Stereo- and Regioselective Generation of Alkenyl Zinc Reagents via Titanium-Catalyzed Hydrozincation of Internal Acetylenes” Y. Gao, K. Harada, T. Hata, H. Urabe, and F. Sato, *J. Org. Chem.*, **60**, 290 (1995).
- “Synthetic Application of Titanabicycles Generated from 1,6- or 1,7-Dienes, Enynes, and Diynes and (η^2 -Propene)Ti(O-*i*-Pr)₂” H. Urabe, T. Hata, and F. Sato, *Tetrahedron Lett.*, **36**, 4261 (1995).

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